10/697,263

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=> d his

     (FILE 'HOME' ENTERED AT 15:24:46 ON 03 MAY 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:25:12 ON 03 MAY 2004
L1       1194984 S KINASE?
L2         26686 S "MYOSIN LIGHT CHAIN"
L3          3175 S "MLCK"
L4         27074 S L2 OR L3
L5          1266 S L4 AND (HOMOLOG? OR SUBFAMIL?)
L6           654 S L1 AND L5
L7       6504283 S CLON? OR EXPRESS? OR RECOMBINANT
L8           337 S L6 AND L7
L9           146 S HUMAN AND L8
L10           93 DUP REM L9 (53 DUPLICATES REMOVED)
L11          129 S "VALINE 68" OR "VAL 68" OR "V68"
L12          609 S "ALANINE 68" OR "ALA 68" OR "A68"
L13           20 S "SERINE 545" OR "SER 545" OR "S545"
L14            5 S "ALANINE 869" OR "ALA 869" OR "A869"
L15          764 S L11 OR L12 OR L13 OR L14
                 E WEI M H/AU
L16          134 S E3-E4
                 E DIFRANCESCO V/AU
L17          111 S E3-E4
                 E BEASLEY E M/AU
L18          291 S E3
L19         1279 S L15 OR L16 OR L17 OR L18
L20            1 S L9 AND L19
L21          764 S L15 AND L19
L22            1 S L6 AND L19
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PASSWORD:
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 NEWS  3  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS  4  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS  5  FEB 05  German (DE) application and patent publication number format
                  changes
 NEWS  6  MAR 03  MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03  FRANCEPAT now available on STN
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 NEWS 10  MAR 29  WPIFV now available on STN
 NEWS 11  MAR 29  No connect hour charges in WPIFV until May 1, 2004
 NEWS 12  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA
 NEWS 13  APR 26  PROMT: New display field available
 NEWS 14  APR 26  IFIPAT/IFIUDB/IFICDB: New super search and display field
                  available
 NEWS 15  APR 26  LITALERT now available on STN
 NEWS 16  APR 27  NLDB: New search and display fields available

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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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=> s kinase?
L1     1194984 KINASE?

=> "myosin light chain"
"MYOSIN IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s "myosin light chain"
L2       26686 "MYOSIN LIGHT CHAIN"

=> s "MLCK"
L3        3175 "MLCK"

=> s l2 or l3
L4       27074 L2 OR L3

=> s l4 and (homolog? or subfamil?)
L5        1266 L4 AND (HOMOLOG? OR SUBFAMIL?)

=> s l1 and l5
L6         654 L1 AND L5

=> s clon? or express? or recombinant
   5 FILES SEARCHED...
L7     6504283 CLON? OR EXPRESS? OR RECOMBINANT

=> s l6 and l7
L8         337 L6 AND L7

=> s human and l8
L9         146 HUMAN AND L8

=> dup rem l9
PROCESSING COMPLETED FOR L9
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L10 93 DUP REM L9 (53 DUPLICATES REMOVED)

=> d 1-93 ibib ab

L10 ANSWER 1 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:85984 HCAPLUS
DOCUMENT NUMBER: 140:194432
TITLE: **Human** prostate cancer marker genes associated with various metastatic stages identified by gene profiling, and related compositions, kits, and methods for diagnosis, prognosis and therapy
INVENTOR(S): Schlegel, Robert; Endege, Wilson O.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 131 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004009481	A1	20040115	US 2002-166883	20020611
US 2004009481	A1	20040115	US 2002-166883	20020611

PRIORITY APPLN. INFO.: US 2001-297285P P 20010611
US 2002-166883 A 20020611

AB The invention relates to compns., kits, and methods for diagnosing, staging, prognosing, monitoring and treating **human** prostate cancers. A variety of marker genes are provided, wherein changes in the levels of **expression** of one or more of the marker genes is correlated with the presence of prostate cancer. In particular, three sets of the marker genes set, corresponding to 11617 GenBank Accession Nos. (only 2168 new submissions) and 15 SEQ IDs, are identified by transcription profiling using RNA derived from clin. samples, that were **expressed** at least 2-fold or greater than the normal controls. Using TNM staging approach, these markers are divided to three groups, ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the liver (M stage); ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the bone (M stage); and ones can be used to determine whether prostate cancer has metastasized, or is likely to metastasize, to the lymph nodes (N stage and/or M stage). The invention also relates to a kit for assessing the specific type of metastatic prostate cancer, e.g., cancer that has metastasized to the liver, bone or lymph nodes. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 2 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2004-07975 BIOTECHDS
TITLE: Inhibiting neuronal cell death using neuronal marker genes and proteins, useful for diagnosing, preventing and/or treating optic nerve degeneration, Alzheimer's disease, diabetic retinopathy, Parkinson's disease and glaucoma; neuronal cell death inhibition and antibody for use in disease gene therapy
AUTHOR: ZACK D J; HACKAM A S
PATENT ASSIGNEE: UNIV JOHNS HOPKINS
PATENT INFO: WO 2004007674 22 Jan 2004
APPLICATION INFO: WO 2003-US21737 14 Jul 2003
PRIORITY INFO: US 2002-395460 12 Jul 2002; US 2002-395460 12 Jul 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-122915 [12]

AB DERWENT ABSTRACT:

NOVELTY - Inhibiting neuronal cell death comprises administering to a subject an isolated molecule comprising an antibody variable region which specifically binds to a neuronal marker (NM1) protein, whereby neuronal cell death is inhibited.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a method of preventing neuronal cell death in a mammal, comprising administering to the mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker (NM2) protein and/or the NM2 protein, whereby neuronal cell death in the mammal is inhibited or prevented; (2) method of identifying regions of neuronal cell death in a patient, comprising administering to a patient a molecule comprising an antibody variable region which specifically binds to NM1 protein, wherein the molecule is bound to a detectable moiety, and detecting the detectable moiety in the patient, thereby identifying regions of neuronal cell death; (3) a method of screening for neuronal cell death in a patient, comprising contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to NM1 protein, or detecting an NM1 protein or a nucleic acid encoding the NM1 protein in a body fluid collected from the patient, wherein detection of cross-reactive material in the body fluid with the molecule indicates neuronal cell death in the patient; (4) a method of promoting neuronal cell death in a patient, comprising administering to a patient in need of neuronal cell death an NM1 protein or a nucleic acid molecule encoding the NM1 protein, whereby neuronal cell death in the patient is stimulated; and (5) a method to identify candidate drugs for treating neuronal cell death, comprising contacting cells which **express** one or more NM1 and/or NM2 genes and/or proteins with a test compound, determining **expression** or activity of the one or more NM1 genes and/or proteins by hybridization of mRNA of the cells to a nucleic acid probe which is complementary to the mRNA, and identifying a test compound as a candidate drug for treating neuronal cell death if it decreases **expression** or activity of the one and/or more NM1 and/or NM2 genes or proteins.

WIDER DISCLOSURE - Also disclosed are NM nucleic acids, polypeptides, host cells, vectors and antibodies used in the methods of the invention.

BIOTECHNOLOGY - Preferred Method: The neuronal marker (NM1) protein is ESTsMrn 40262, Mus musculus calcium binding protein 1, M musculus ribonucleic acid binding protein Sl Rnpsl, ESTsMm 10622, contactin 3Mm 2968, Mus musculus glycoprotein 38, neurochondrinMm 43445, no matchS, Mus musculus crystallin beta A4, S100 protein beta polypeptide neuralMm 829, Mm 37346, chromogranin BMm 1339, no match111, glial fibrillary acidic proteinMm 1239, Sugano mouse brain mncb MNCb 4842 5, Mus musculus Ly6 neurotoxin 1 , ESTsMm 22801, **Human** Chromosome 7 **clone** RPl 1 297N5, proteolipid protein myelin Mm 1268, ESTs Weakly similar to F2 alpha prostaglandin regulatory protein M musculus Mm 29860, ESTsMm 28098, Mus musculus fibroblast growth factor 13, glutamate receptor ionotropic NMDAl zeta 1 Mm 3292, amyloid beta A4 precursor protein binding family A member 2Mm 4657, ESTsMm 41808, Mus musculus zinc finger transcription factor Kaiso mRNA complete cdsMm 100832, R norvegiens mRNA for pro alpha 1 collagen type III, heat shock protein 25 IcDa 2 cardiovascular Mm 103612, Mus musculus hypothetical protein 154, transcription factor 4Mm 4269, ESTs Highly similar to ATP SYNTHASE DELTA CHAIN MITOCHONDRIAL PRECURSOR Rattus norvegicus Mm 22514, M musculus vacuolar proton translocating ATPase 100 WDa subunit isoform al I, selenoprotein P plasma IMm 22699, solute carrier family 2 facilitated glucose transporter member 3Mm 3726, ESTsMm 33880, ESTsMm 34740, ESTsMrn 29832, cathepsin DMm 2147, secretogranin HIMm 2386, Mouse mRNA for neural cell adhesion molecule, Mus musculus glutathione S transferase mu 1 , no match98, R norvegicus microtubule associated protein 1A MAPlA, M musculus selenoprotein P, Mus musculus secreted phosphoprotein 1, ESTsMrn 27363, ESTs Moderately similar to CALPONIN ACIDIC ISOFORM Rattus norvegicus Mm 22171 , collapsin response mediator protein IMm 22695, insulin like

growth factor binding protein 5Mm 578, ESTs Highly similar to neuroglycan C precursor R norvegiens Mm 38496, Mus musculus melastatin 1 Mlsnl , ceruloplasminMm 13787, ESTs Weakly similar to delta 6 fatty acid desarurase M musculus Mm 30158, ESTsMm 43499, Ratrus norvegicus CD44 protein, M musculus G protein coupled receptor 37, UI M BH3 aun e 05 O Ul si NlH BMAP M S4, M musculus secreted acidic cysteine rich glycoprotein, nuclear receptor co represser IMm 88061, ribosomal protein mitochondrial S7Mm 29902, Mm 104779, tropomodulin 2Mm 44216, M musculus insulin like growth factor binding protein 5, Mus musculus secreted acidic cysteine rich gly, Homo sapiens KIAAl 077 protein, stearoyl Coenzyme A desaturase 2Mm 298, M musculus dickkopf **homolog** 3 Dkk 3, Mus musculus transketolase Tkt, L0283F10 3 Mouse Newborn Ovary cDNA Library, Mus musculus neuron specific gene family member 2, prostaglandin D2 synthase 21 kDa brain Mm 1008, Mus neural cell adhesion molecule NCAM 140, Mouse brain specific small RNA, Mus musculus protein phosphatase 2, farnesyl diphosphate farnesyl transferase IMm 3204, Mmusculus proteolipid M6B isoform TMD psi M6B, Mouse brain neurofilament L, brain protein E46Mm 4098, Rattus norvegicus Spinophilin mRNA, ESTsMm 5258, ESTsMm 17436, Mouse heat shock protein hsp84, no match71 , Mm 29846, R norvegicus n chimaerin, ESTsMm 10641 , Mus musculus protein tyrosine phosphatase, Mm 100761, H sapiens transmembrane 4 superfamily member 7, H sapiens chromosome 3 **clone** RPl 1 19E8 map 3p, ESTsMm 26680, UIM BH3 avk f 09 O UI si NIH BMAP M S4, ESTs Moderately similar to PRAJAl M musculus Mm 41711, Homo sapiens RNA binding protein BRUNOL4, actin beta cytoplasmicMm 103618, NCK associated protein IMm 25203, Mus musculus transcription factor 4 Tcf4, ESTsMm 39985, Mouse mRNA for OSF 1, ESTsMm 27030, Mouse cysteine rich glycoprotein, ESTsMm 71533, H sapiens membrane glycoprotein M6, **Human** hBOIT brain type organic ion transporter, dickkopf **homolog** 3 Xenopus laevis Mm 55143, no match23, DNA segment Chr 19 Wayne State University 55 **expressedMm** 29835, Mus musculus calpain 4, ESTs Highly similar to EXCITATORY AMINO ACID TRANSPORTER 1 M musculus Mm 33356, Ca2 dependent activator protein for secretionMm 5058, oxidative stress inducedMm 9846, adducin 1 alpha Mm 29052, ESTs Weakly similar to ORF YKR092c S cerevisiae Mm 24356, Mus musculus membrane protein TMS 2 mRNA complete cdsMm 29344, R norvegicus neurodegeneration associated protein 1, glutamine synthetaseMm 2338, ESTsMm 24254, Mus musculus clusterin, Mouse beta rubulin gene M beta 4 3 end, Mus musculus vimentin, Homo sapiens mRNA cDNA DKFZp5S6Nl 922, ESTsMm 27467, Mus musculus mRNA for profilin II pfn2 gene Mm 20399, protein L isoaspartate D aspartate O methyltransferase IMm 25293, ESTsMm 41819, ESTs Weakly similar to pi 90 B M musculus Mm 13835, anti oxidant protein 2Mm 6587, Mus musculus sulfated glycoprotein 2 isoform 2, ESTs Highly similar to zyginl R norvegiens Mm 5264, calmodulinMm 2648, and Homo sapiens membrane glycoprotein M6. The NM2 protein is NM Mus musculus retinal S antigen; Mus musculus neural retina leucine zipper gene; M musculus photoreceptor specific protein PSP G145; IMAGE 4507893 5; Mus musculus domesticus phosducin; IMAGE 4507284 5; Danio rerio brain type fatty acid binding protein; M musculus X linked juvenile retinoschisis protein; M musculus guanine nucleotide binding protein beta 1 Gnbl; Mus musculus TPA regulated locus; Mouse nuclear protein mdm 1; IMAGE 4511806 5; M musculus male germ cell associated **kinase**; heat shock protein 60 kDaMm 1777; no match17; NCI CGAP BC3 Mus musculus cDNA **clone** IMAGE 3976794; no homolo; Homo sapiens CGI45 protein; ESTsMm 44103; Mouse opsin MOPS; IMAGE 4225062 5; Mm 100212; H sapiens fer fps fes related tyrosine **kinase** phosphoprotein NCP94 FER; IMAGE 4505626 5 602393946F1 NIH MGC 94; solute carrier family 12 member 2Mm 4168; Mus musculus BUB2 like protein 1 HBLPl mRNA complete cdsMm 104771; hemoglobin Y beta like embryonic chainMm 35830; erythrocyte protein band 4 IMm 30038; no niatch55; Mus musculus MYLE protein niRNA complete cdsMrn 41091 ; RIKEN full length enriched adult male hypothalamus musculus cDNA **clone** A230050E13; NCI CGAP Mamo Mus IMAGE 3500058; Mus musculus mRNA for GTP binding protein drg2 gene Mm 41803; Homo sapiens mRNA for KIAAl 549 protein; Mus musculus karyopherin importin alpha 2 Kpna2; UI M BZl bkv b 01 0 UI3; no match B; ESTsMm 939; Mus musculus cDNA sequence

AF244542; IMAGE 1348390 5; solute carrier family 30 zinc transporter member 3Mm 1396; no match110; Mus musculus homeodomain protein crx; prominin Mm 6250; no homol3; IMAGE 1279184 5; **Human** microfibril associated glycoprotein 4; Mm 70462; no match A; Rattus sp mRNA for BHF 1 ; ribosomal protein S24Mm 16775; Stratagene mouse Tcell 937311 IMAGE 1002041; NCI CGAP Kidl4 Mus IMAGE 4236354 5; R norvegicus retinoblastoma binding protein 9; Mus musculus exostoses multiple 1 Extl; selectin endothelial cell ligandMm 488; ESTs Weakly similar to HYPOTHETICAL 16 1 KD PROTEIN IN SEC 17 QCRl INTERGENIC REGION Saccharomyces cerevisiae Mm 27114; ESTs Highly similar to KIAA0824 protein H sapiens Mm 34579; Mus musculus ribosomal protein LlOA RpIlOa; R norvegicus ribonucleoprotein F; **clone** 1110007F23; no match38; M musculus Srp20 gene; homeodomain interacting protein **kinase** 2Mm 20934; FSHD region gene IMm 67; UIM BH3 an c 10 O UI si NIH BMAP M S4; Homo sapiens CED 6 protein CED 6; Mus musculus RIKEN **clone** 0610009E22; RAB18 member RAS oncogene familyMm 22660; no match5; Mus musculus prominin Prom; ribosomal protein L12Mm 70127; ESTs Highly similar to ELONGATION FACTOR 1 DELTA Homo sapiens Mm 21086; ESTs Highly similar to HYPOTHETICAL 37 2 KD PROTEIN C12C2 09C IN CHROMOSOME I Schizosaccharomyces pombe Mm 21383; **clone** 3021401C12; M musculus very long chain acyl CoA dehydrogenase; vitronectinMm 3667; ESTs Weakly similar to LIV 1 protein H sapiens Mm 41214; Mus musculus dopamine receptor 4; no match7; ATPase H transporting lysosomal vacuolar proton pump noncatalytic accessory protein 1 110 160 IcDa Mm 20869; Rattus norvegicus partial mRNA for CRMl protein; eukaryotic translation elongation factor 1 alpha IMm 16317; **Human** karyopherin beta2 importin; ESTs Moderately similar to hypothetical protein H sapiens Mm 22878; Homo sapiens PAC **clone** RP4 687Kl; UIM AOl aeh e 11 O UI rl NIH BMAP MPG N; high mobility group protein 14Mm 2756; ESTsMm 31374; R norvegicus aryl hydrocarbon interacting protein like 1; UIM CGOp bmu h 08 O UI si NIH BMAP Ret4 S2; RABlO member RAS oncogene familyMm 9455; Mus musculus early development regulator 2; no match83; Mus musculus topoisomerase DMA II beta; alpha tubulin; Homo sapiens MTAl Ll ; retinitis pigmentosa GTPase regulator interacting protein 1 Mm 21662; Mus musculus FXYD dom containing ion transport regulator 5; Mus musculus cytochrome P450 3A25 CYP3A25 mRNA complete cdsMm 26993; IMAGE 4505626 5; RNA polymerase II transcriptional coactivatorMm 966; ESTs Highly similar to CAAX prenyl protease H sapiens Mm 34399; Soares mammary gland NbMMG IMAGE 1347586; **clone** 2700067D09; ESTs Weakly similar to defline not available 5901802 D melanogaster Mm 35127; torsin family 1 member AMm 29151 ; Mm 23086; M musculus brain cyclic nucleotide gated K; Mus musculus N myc downstream regulated 1 ; Homo sapiens splicing factor 3b subunit 3; Mus musculus mRNA for Lim homeodomain protein IsletlMm 42242; Mouse mRNA for syntaxin 3D 1 ; Mus musculus chromosome 7 **clone** 19K5; ES18 proteinMm 23296; ESTs Highly similar to K1AA0729 protein H sapiens Mm 13148; ESTsMm 33949; Rat transcription factor RZR beta gene; ESTs Moderately similar to hypothetical protein H sapiens Mm 30235; Homo sapiens KIAA0009 gene product; no match X; ESTs Moderately similar to **MYOSIN LIGHT CHAIN** KTNASE Dictyostelium discoideum Mm 1881; serum glucocorticoid regulated **kinaseMm** 28405; ESTs Weakly similar to cappuccino D melanogaster Mm 41762; regulator of G protein signaling 9Mm 38548; ESTsMrn 34351 ; ESTsMm 32460; Mm 44404; ESTsMm 37515; Mus musculus cytochrome P450 2f2 Cyp2f2; Finkel Biskis Reilly murine sarcoma virus FBR MuSV ubiquitously **expressed** fox derived Mm 4890; guanylate cyclase activator 1 a retina Mm 16224; **human** CRX control; adducin 2 beta Mm 104155; mouse CRX control; NRL control; Mus musculus ELOVL4; Mus musculus N myc downstream regulated 3; lactate dehydrogenase 1 A chainMm 26504; ESTs Moderately similar to stromelysin PDGF responsive element binding protein transcription factor M musculus Mm 38372; ESTsMm 11285; M musculus chr 10 **clone** RP21 39C4; ESTs Highly similar to 40 KD PEPTIDYL PROLYL CIS TRANSISOMERASE Homo sapiens Mm 30242; NIH BMAP Ret4 S2 Mus UIM CGOp big e 08 O UI3; Soares mammary gland NMLMG IMAGE 3467149; glycosylphosphatidylinositol 1 **homolog human** Mm 6354; Rattus norvegiens NMDA receptor

subunit NR2; ESTsMm 33788; Mus musculus hexokinase 1 HkI; inosine 5 phosphate dehydrogenase 2Mm 6065; N myc downstream regulated 3Mm 36775; no match V; villin 2Mm 4551 ; Rattus norvegiens TM6P1 TM6P1; Mus musculus mRNA for heterogeneous nuclear ribonucleoprotein HMm 21740; ESTsMm 103333; Mus musculus retinal taurine transporter, Mus musculus poly rC binding protein; ESTs Weakly similar to nuclear poly C binding protein M musculus Mm 29707; ESTs Weakly similar to similar to 1 acyl glycerol 3 phosphate acyltransferases C elegans Mm 24117; Mm 27013 ; pre B cell leukemia transcription factor 3Mm 7331 ; ESTsMm 21299; Mus musculus kinectin 1; Mus musculus drebrin A mRNA complete cdsMm 104044; H3087H01 5 NlA Mouse 15K cDNA **Clone** Set; SAC483 Mouse el 4 5 developing pituitary gland; **cloneE130113K08**; Mus musculus major histocompatibility locus class II region Fas binding protein Daxx DAXX gene partial cds Bingl BINGl tapasin tapasin RaIGDS like factor RLF KE2 KE2 BING4 BING4 betal 3 galactosyl transferase betal 3 galactosylMm 20926; Mus musculus aquaporin 1; acyl Coenzyme A dehydrogenase very long chainMm 18630; Mouse proprotein convertase 4; M musculus activating transcription factor 4 Atf4; guanine nucleotide binding protein beta 5Mm 4702; phosducin control; ESTsMm 38578; Barstead bowel MPLRB9 IMAGE 1095982; M musculus stromal cell derived factor recep; ESTs Weakly similar to E04F6 2 gene product C elegans Mm 18889; IMAGE 963149 5; syntaxin binding protein 1 Mm 3129; solute carrier family 16 monocarboxylic acid transporters member IMm 9086; ESTs Highly similar to TRICARBOXYLATE TRANSPORT PROTEIN PRECURSOR Rattus norvegicus Mm 22679; Bcl2 HkeMrn 3882; Soares mousep3NMF19 5 IMAGE 493296; Mus musculus beta galactosidase complex; H sapiens ADP ribosylation factor binding protein GGA2; Mrn 31266; IMAGE 560050 5; Mus musculus DXHXS6673E protein DXHXS6673E mRNA complete cdsMm 23458; M musculus mRNA for hair keratin mHbo; Mus musculus thyroglobulin; ESTs Moderately similar to KIAA0956 protein H sapiens Mm 11428; H3050H05 3 NIA Mouse 15K cDNA **Clone** Set; ESTs Moderately similar to signal recognition particle 54K protein M musculus Mm 32508; Mouse PSD 95 SAP90A; ESTsMm 29308; alkaline phosphatase 2 liverMm 1265; Homo sapiens 12 seeders BAC RP11 19El 8; ESTsMm 41269; ESTsMm 86724; Homo sapiens 12ql3 1 PAC RPCIl 228Pl 6; serine threonine **kinase** receptor associated proteinMm 22584; UIM BZO axl a 11 O UI si NIH BMAP MHI2; Mus musculus poly rC binding protein 2; IMAGE 4503171 5; ESTsMm 35430; activating transcription factor 4Mm 641 ; Mouse serine threonine phosphatase 2C; GAPDH control; **Human** mRNA for K1AA0299; ESTs Weakly similar to proline rich protein M musculus Mm 41665; megakaryocyte associated tyrosine **kinaseMm** 2918; homer neuronal immediate early gene 2Mm 228; peroxisomal farnesylated proteinMm 29198; blank; zinc finger protein 238Mm 27962; ESTs Highly similar to PHENYLALANYLTRNA SYNTHETASE BETA CHAIN CYTOPLASMIC Saccharomyces cerevisiae Mm 27403; Rat microtubule associated protein 2 MAP2; timeless **homolog** Drosophila Mrn 6458; kinectin IMm 3110; phosphatidylinositol membrane associatedMm 1860; R norvegiens CDP diacylglycerol synthase; Homo sapiens DKFZp434Al 32; Mus musculus hematopoietic zinc finger; mitogen activated protein **kinase kinase** 7Mm 3906; H3110G03 3 NIA Mouse 15K cDNA; ESTs Highly similar to HYPOTHETICAL 47 9 KD PROTEIN B0303 3 IN CHROMOSOME III Caenorhabditis elegans Mm 30147; ESTs Highly similar to CELL GROWTH REGULATING NUCLEOLAR PROTEIN M museums Mm 28560; no match W; Mouse endogenous murine leukemia virus polytropic provirus DNA; **clonelll0013A05**; aryl hydrocarbon receptorMm 4452; peroxisome proliferator activated receptor alphaMm 1373; Mus musculus LAG protein Lag Rattus NMDA receptor glutamate binding subunit; Mus musculus syntaxin binding protein 1 ; Mus musculus MAP **kinase** phosphatase 6; Rattus norvegiens retina specific protein PAL; no match33; Mus musculus myc box dependent interacting pro; Murine leukemia virus ervl envelope protein; cytochrome c oxidase subunit Vila 3Mm 2151 ; proteasome prosome macropain subunit alpha type 3Mm 1007; Homo sapiens mRNA cDNA DKPZp434Nl 615; Mus musculus TCR beta locus; ESTs Weakly similar to LOK M musculus Mm 74661 ; small inducible cytokine **subfamily** A member 22Mm 12895; ESTsMm 23682; no match I; no match H; high mobility group protein

I isoform CMm 3953; protein **kinase** cAMP dependent catalytic alphaMm 22479; Mus musculus phosphatidylinositol membrane associated; no match G; Mouse heparin binding epidermal growth factor like; Homo sapiens cDNA DKFZpS 86B0924; Mouse magnesium dependent protein; ESTs Weakly similar to ZWlO interactor Zwint H sapiens Mm 38994; ESTsMm 30480; H sapiens ADP ribosylation factor GTPase activating protein 1; Mus elongation of very long chain fatty acids; Mouse Y box binding protein 1 DNA binding MSY 1 ; Homo sapiens KIAA0249 gene product; Mus musculus Ran binding protein 2; Mus musculus histidine decarboxylase cluster; Homo sapiens cDNA FLJ21612 fis **clone** COL07355; UIM BH2 3 aqc g 10 O UI5; Rattus norvegiens APP binding protein 1 ; Mus musculus beta site APP cleaving enzyme; DNA methyltransferase cytosine 5 Mm 7814; no match66; ESTs Weakly similar to Lpi2p S cerevisiae Mm 21859; R norvegicus phosphatidylinositol synthase; ribonuclease L 2 5 oligoisoadenylate synthetase dependent inhibitorMm 5831; MTB 104074; H sapiens protein phosphatase 2A regulatory subunit B; H3147A11 5 NlA Mouse 1 SK cDNA **Clone** Set; Mus musculus Y box transcription factor; Mouse gene for basigin; Homo sapiens mRNA for FLJ00042 protein; R norvegicusnupl 55 nucleoporin 155kD; tubby like protein 1 Mm 42102; R norvegicus RNA binding protein SiahBP; UI M BZO axj h 06 O UI 3; and Mus musculus pyruvate **kinase** 3.

ACTIVITY - Ophthalmologic; Nootropic; Neuroprotective; Antidiabetic; Anticonvulsant; Vulnerary; Antiparkinsonian; Cytostatic. No biological data given.

MECHANISM OF ACTION - Gene-Therapy.

USE - The methods and compositions of the present invention are useful for the diagnosis, prevention and/or treatment of diseases or conditions associated with neuronal cell death, such as optic nerve degeneration, Alzheimer's disease, diabetic retinopathy, Huntington's disease, spinal cord injury, Parkinson's disease, glaucoma, neuronal tumor and age-related macular degeneration (claimed).

ADMINISTRATION - Routes of administration of the pharmaceutical compositions include intramuscular, intraperitoneal, intravenous, subcutaneous, intrarectal, transdermal and intranasal. No dosages given.

EXAMPLE - No relevant example given. (163 pages)

L10 ANSWER 3 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:287758 HCAPLUS
DOCUMENT NUMBER: 140:302345
TITLE: Genes showing altered patterns of **expression** in the central nervous system in multiple sclerosis and their diagnostic and therapeutic use
INVENTOR(S): Dangond, Fernando; Hwang, Daehee; Gullans, Steven R.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028339	A2	20040408	WO 2003-US29451	20030925

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,

GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2002-414219P P 20020927
AB The present invention identifies a number of gene markers whose **expression** is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

L10 ANSWER 4 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:162616 HCAPLUS
DOCUMENT NUMBER: 140:212062
TITLE: Use of murine genomic regions identified to be involved in tumor development for the development of anti-cancer drugs and diagnosis of cancer
INVENTOR(S): Touw, Ivo Paul; Delwel, Hendrik Rudolf; Lowenberg, Bob; Valk, Peter Jacobus Maria
PATENT ASSIGNEE(S): Erasmus University Medical Center Rotterdam, Neth.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004016317	A1	20040226	WO 2003-NL583	20030814
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1393776	A1	20040303	EP 2002-78358	20020814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: EP 2002-78358 A2 20020814
US 2002-252132 A2 20020919

AB The present invention relates to murine genomic regions identified by retroviral insertional tagging of mice as being involved in tumor development, in particular leukemia development, as well as their **human homologs**. In vivo retroviral mutagenesis using the Graffi-1.4 murine leukemia virus complex to identify novel routes for the pathogenesis of acute myeloid leukemia (MuLV) by identifying the disease genes specifically involved. Seventy-nine candidate disease genes in common virus integration sites (CIS) and 15 genes of which family members were previously found to be infected are reported. Applying virus LTR-specific inverse-PCR and RT-PCR combined with automated sequencing on CasBr-M MuLV induced myeloid leukemias, 126 virus integration sites were **cloned**. The use of these genomic regions for the identification and development of anti-cancer drugs, such as small mol. inhibitors, antibodies, ribozymes, antisense mols., and RNA interference (RNAi) mols., that are effective in reducing or eliminating the tumorigenic effects of genetic transformations in these genomic regions and/or eliminating the tumorigenic effects of **expression** products thereof is also provided. The invention further relates to these anti-cancer drugs and to their use as pharmaceutical reagents for the treatment of cancer, as well as to pharmaceutical compns. comprising one or more of said pharmaceutical

reagents and to methods for the treatment of cancer using said pharmaceutical compns., in particular to methods of gene therapy. In yet further aspects, the invention relates to nucleic acids, to antibodies capable of binding specifically to murine genomic regions and to **expression** products thereof, to the use of said nucleic acids or antibodies as diagnostic reagents for the diagnosis of cancer, as well as to diagnostic compns. comprising one or more of said diagnostic reagents and to methods for the diagnosis of cancer using said diagnostic compns.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:119871 HCAPLUS
DOCUMENT NUMBER: 140:158535
TITLE: Gene **expression** profiling of Gleason grades 3 and 4/5 prostate cancer for identifying tumor markers, and diagnostic and therapeutic uses
INVENTOR(S): Mahadevappa, Mamatha; Zhang, Zhaomei; Warrington, Janet A.; Palma, John F.; Caldwell, Mitchell C.; Chen, Zuxiong; Fan, Zhenbin; Mcneal, John E.; Nolley, Rosalie; Stamey, Thomas A.
PATENT ASSIGNEE(S): Affymetrix, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004029151	A1	20040212	US 2003-411537	20030409

PRIORITY APPLN. INFO.: US 2002-371304P P 20020409

AB Many genes are affected in prostate cancers which have not been previously identified. This includes genes that have been up-regulated or down-regulated. Monitoring the **expression** levels of these genes is useful to identify the existence of prostate cancer. Down-regulated and up-regulated genes have been identified in Gleason grades 3 and 4/5 cancer, using the gene profile from benign prostatic hyperplasia (BPH) as control tissue. Hepsin appears to be the most promising, as its mRNA was highly up-regulated in neoplastic prostate tissue. The regulated genes can be used diagnostically, prognostically, therapeutically, and for drug screening.

L10 ANSWER 6 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:59653 HCAPLUS
DOCUMENT NUMBER: 140:126701
TITLE: Cellular gene **expression** monitoring for **human** cytomegalovirus (HCMV) infection for diagnostic and drug screening applications
INVENTOR(S): Zhu, Hua; Gingeras, Thomas R.; Shenk, Thomas
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 26 pp., Cont. of U.S. Ser. No. 377,907.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004014027	A1	20040122	US 2001-950024	20010912

PRIORITY APPLN. INFO.: US 1999-377907 A1 19990820

AB Certain **human** genes have been found to be induced or repressed in host cells infected with HCMV. A large set of such genes has been identified. These have diagnostic use in determining the extent of tissue damage caused by the infection as well as in determining the stage of disease progression of the HCMV infection. Such genes are likely those involved in mediating the pathol. of the infected tissues. Thus by identifying agents which are able to reverse the induction or repression of such genes, one can find candidate therapeutic agents for use in treating and or preventing HCMV-caused disease pathologies. Specifically disclosed are 258 mRNAs (with GenBank Accession Number provided) identified from microarray of about 6600 mRNA isolated from primary **human** fibroblast infected with HCMV strain AD169, whose levels are changed by a factor of 4 or more (124 increased, 134 decreased) in response to HCMV infection (after infection but before the onset of viral DNA replication). Several of these mRNAs are claimed to encode gene products that might play key roles in virus-induced pathogenesis, which include HLA-E, Ro/SSA, lipocortin-1, cPLA2, COX-2 and thrombospondin-1.

L10 ANSWER 7 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:39587 HCAPLUS
DOCUMENT NUMBER: 140:92056
TITLE: Analysis of gene **expression** profiles using neural networks in the diagnosis of cancers and in the selection of targets for cancer therapy
INVENTOR(S): Khan, Javed; Ringner, Markus; Peterson, Carsten; Meltzer, Paul
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 53 pp., Cont.-in-part of U.S. Ser. No. 133,937.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004009154	A1	20040115	US 2002-159563	20020531
US 2003207278	A1	20031106	US 2002-133937	20020425

PRIORITY APPLN. INFO.: US 2002-133937 A2 20020425
AB Anal. of gene **expression** profiles using neural networks is used to identify genes **expressed** in specific neoplasms for use in diagnosis and in the selection of treatments. The gene selection functions to characterize a cancer when the **expression** of that gene selection is compared to the identical selection from a noncancerous cell or a different type of cancer cell. The invention also includes a method of targeting at least one product of a gene that includes administration of a therapeutic agent. The invention also includes the use of a gene selection for diagnosing a cancer.

L10 ANSWER 8 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003612555 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14570871
TITLE: Regulatory mechanism of Dictyostelium **myosin light chain kinase** A.
AUTHOR: Tokumitsu Hiroshi; Hatano Naoya; Inuzuka Hiroyuki; Ishikawa Yumi; Uyeda Taro Q P; Smith Janet L; Kobayashi Ryoji
CORPORATE SOURCE: Department of Signal Transduction Sciences, Kagawa Medical University, 1750-1 Miki-cho, Kita-gun, Kagawa 761-0793, Japan.. tokumit@kms.ac.jp
SOURCE: Journal of biological chemistry, (2004 Jan 2) 279 (1) 42-50.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20031230
Last Updated on STN: 20040304
Entered Medline: 20040303

AB In this study, we examined the activation mechanism of Dictyostelium **myosin light chain kinase** A (**MLCK**-A) using constitutively active Ca2+/calmodulin-dependent protein **kinase kinase** as a surrogate **MLCK**-A **kinase**. **MLCK**-A was phosphorylated at Thr166 by constitutively active Ca2+/calmodulin-dependent protein **kinase kinase**, resulting in an approximately 140-fold increase in catalytic activity, using intact Dictyostelium myosin II. **Recombinant** Dictyostelium myosin II regulatory light chain and Kemptamide were also readily phosphorylated by activated **MLCK**-A. Mass spectrometry analysis revealed that **MLCK**-A **expressed** by Escherichia coli was autophosphorylated at Thr289 and that, subsequent to Thr166 phosphorylation, **MLCK**-A also underwent a slow rate of autophosphorylation at multiple Ser residues. Using site-directed mutagenesis, we show that autophosphorylation at Thr289 is required for efficient phosphorylation and activation by an upstream **kinase**. By performing enzyme kinetics analysis on a series of **MLCK**-A truncation mutants, we found that residues 283-288 function as an autoinhibitory domain and that autoinhibition is fully relieved by Thr166 phosphorylation. Simple removal of this region resulted in a significant increase in the kcat of **MLCK**-A; however, it did not generate maximum enzymatic activity. Together with the results of our kinetic analysis of the enzymes, these findings demonstrate that Thr166 phosphorylation of **MLCK**-A by an upstream **kinase** subsequent to autophosphorylation at Thr289 results in generation of maximum **MLCK**-A activity through both release of an autoinhibitory domain from its catalytic core and a further increase (15-19-fold) in the kcat of the enzyme.

L10 ANSWER 9 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:942764 HCAPLUS
DOCUMENT NUMBER: 140:3792
TITLE: Genes **expressed** in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XA38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-374547P P 20020423
US 2002-420784P P 20021024
US 2002-421043P P 20021025
US 2002-424680P P 20021108
WO 2002-US38221 A 20021112

AB Genes whose **expression** is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal.

L10 ANSWER 10 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:187089 HCAPLUS
DOCUMENT NUMBER: 138:219711
TITLE: Differentially expressed gene expression profiles in human glomerular diseases
INVENTOR(S): Munger, William E.; Falk, Ronald; Sun, Hongwei; Sasai, Hitoshi; Waga, Iwao; Yamamoto, Jun
PATENT ASSIGNEE(S): Gene Logic, Inc., USA; University of North Carolina At Chapel Hill
SOURCE: PCT Int. Appl., 781 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003016476	A2	20030227	WO 2002-XF25766	20020814

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2003016476	A2	20030227	WO 2002-US25766	20020814
WO 2003016476	A3	20030508		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-311837P P 20010814
WO 2002-US25766 A 20020814

AB The present invention is based on the elucidation of global changes in gene expression in peripheral blood leukocytes (PBL) of patients with glomerular diseases exhibiting different types of clin. and pathol. features of glomerular nephropathy as compared to normal PBL as well as the identification of individual genes that are differently expressed in PBL of patients with glomerular diseases. The genes and gene expression information may be used as markers for the diagnosis of disease subtype, such as IgA nephropathy, Minimal Change nephrotic syndrome, antineutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA), focal segmental glomerulosclerosis (FSGS), and lupus nephritis. The genes may also be used as markers to evaluate the effects of a candidate drug or agent on tissues, including PBLs, particularly PBLs undergoing activation or PBLs from a patient with glomerular disease. Differential expression of genes between PBLs from patients with glomerular disease and normal PBL samples was determined using the Affymetrix 42K human gene chip set. [This abstract record is one of nine records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 11 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:972197 HCAPLUS
DOCUMENT NUMBER: 140:24173
TITLE: **Human** cDNA sequences and their encoded proteins and diagnostic and therapeutic uses
INVENTOR(S): Alsobrook, John P., II; Anderson, David W.; Baumgartner, Jason C.; Berghs, Constance; Boldog, Ferenc L.; Burgess, Catherine E.; Casman, Stacie J.; Catterton, Elina; Dhanabal, Mohanraj; Edinger, Shlomit R.
PATENT ASSIGNEE(S): Curagen Corporation, USA
SOURCE: PCT Int. Appl., 1503 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 139
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003102159	A2	20031211	WO 2003-US17573	20030604

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004029226	A1	20040212	US 2003-383201	20030306

PRIORITY APPLN. INFO.:
US 2002-385490P P 20020604
US 2002-385615P P 20020604
US 2002-385755P P 20020604
US 2002-386041P P 20020605
US 2002-386355P P 20020606
US 2002-386357P P 20020606

US 2002-386447P P 20020606
US 2002-386459P P 20020606
US 2002-386465P P 20020606
US 2002-386864P P 20020606
US 2002-386701P P 20020607
US 2002-386796P P 20020607
US 2002-386931P P 20020607
US 2002-387078P P 20020607
US 2002-387081P P 20020607
US 2002-387083P P 20020607
US 2002-387429P P 20020610
US 2002-387540P P 20020610
US 2002-387866P P 20020610
US 2002-387606P P 20020611
US 2002-387610P P 20020611
US 2002-387659P P 20020611
US 2002-387668P P 20020611
US 2002-387696P P 20020611
US 2002-387859P P 20020611
US 2002-387934P P 20020612
US 2002-387960P P 20020612
US 2002-388022P P 20020612
US 2002-388096P P 20020612
US 2002-388432P P 20020612
US 2002-388479P P 20020612
US 2002-389123P P 20020613
US 2002-389120P P 20020614
US 2002-389146P P 20020614
US 2002-389742P P 20020617
US 2002-389604P P 20020618
US 2002-389884P P 20020618
US 2002-51874 A 20020116
US 2002-361974P P 20020306
US 2002-93463 A 20020308
US 2002-365034P P 20020315
US 2002-365477P P 20020319
US 2002-365884P P 20020320
US 2002-365984P P 20020320
US 2002-365985P P 20020320
US 2002-366928P P 20020322
US 2002-372018P P 20020412
US 2002-372022P P 20020412
US 2002-374682P P 20020423
US 2002-389143P P 20020614
US 2002-391779P P 20020626
US 2002-403743P P 20020815
US 2002-410755P P 20020913
US 2002-412957P P 20020923
US 2002-420382P P 20021022

AB Disclosed herein are 81 cDNA sequences that encode novel **human** polypeptides that are members of various protein families. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivs., variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel **human** nucleic acids and proteins.

L10 ANSWER 12 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:931518 HCAPLUS
DOCUMENT NUMBER: 140:689
TITLE: Genes showing altered patterns of **expression** in response to inhibition of tyrosine **kinases**

and their use in screening **kinase** inhibitors

INVENTOR(S): Morimoto, Alyssa; Deprimo, Samuel; O'Farrell, Anne-Marie; Smolich, Beverly D.; Manning, William C.; Walter, Sarah A.; Schilling, James Walter, Jr.; Cherrington, Julie

PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097854	A2	20031127	WO 2003-US15711	20030519

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004018528	A1	20040129	US 2003-440464	20030519

PRIORITY APPLN. INFO.:
US 2002-380872P P 20020517
US 2003-448874P P 20030224
US 2003-448922P P 20030224

OTHER SOURCE(S): MARPAT 140:689

AB Genes that are regulated by tyrosine **kinase**-dependent signal transduction pathways are identified as markers for the screening of inhibitors of **kinase** activity. The change in levels of either the protein or mRNA in a suitable test system may be used to assess the effectiveness of a test compound as an inhibitor of a tyrosine **kinase** activity. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine **kinase** activity.

L10 ANSWER 13 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:913280 HCAPLUS

DOCUMENT NUMBER: 139:379453

TITLE: Genes showing altered patterns of **expression** in multiple sclerosis and their diagnostic and therapeutic uses

INVENTOR(S): Dangond, Fernando; Hwang, Daehee

PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA

SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003095618	A2	20031120	WO 2003-US14462	20030507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

US 2004018522 A1 20040129 US 2003-430762 20030506
PRIORITY APPLN. INFO.: US 2002-379284P P 20020509
US 2003-430762 A1 20030506

AB The present invention identifies a number of gene markers whose **expression** is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression. Genes were identified by determination of **expression** profiling. A large number of genes showing altered patterns of **expression** were identified, with the most discriminatory genes being those for: phosphatidylinositol transfer protein, inducible nitric oxide synthase, CIC-1 (CLCN1) muscle chloride channel protein, placental bikunin (AMBP), receptor **kinase** ligand LERK-3/Ephrin-A3, GATA-4, thymopoietin, transcription factor E2f-2, S-adenosylmethionine synthetase, carcinoembryonic antigen, the ret oncogene, a G protein-linked receptor (**clone** GPCR W), GTP- binding protein RALB, tyrosine **kinase** Syk, LERK-2/Ephrin-B1, ELK1 tyrosine **kinase** oncogene, transcription factor SL1, phospholipase C, gastricsin (progastricsin), and the D13S824E locus.

L10 ANSWER 14 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:571236 HCAPLUS
DOCUMENT NUMBER: 139:112797
TITLE: Gene **expression** profiles for diagnostic and prognostic grading of breast cancer
INVENTOR(S): Erlander, Mark G.; Ma, Xiao-Jun; Sgroi, Dennis C.
PATENT ASSIGNEE(S): Arcturus Engineering, Inc., USA; The General Hospital Corporation
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003060470	A2	20030724	WO 2002-US41347	20021220
WO 2003060470	A3	20031113		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

US 2004002067 A1 20040101 US 2001-28018 20011221
US 2003198972 A1 20031023 US 2002-211015 20020801
PRIORITY APPLN. INFO.: US 2001-28018 A 20011221

US 2002-211015 A 20020801

AB This invention relates to the identification and use of gene **expression** patterns (or profiles or "signatures") which are correlated with (and thus able to discriminate between) cells in various stages and/or grades of breast cancer. Broadly defined, these stages are non-malignant vs. malignant, but may also be viewed as normal vs. atypical (optionally including reactive and pre-neoplastic) vs. cancerous. Another definition of the stages is normal vs. precancerous (e.g. atypical ductal hyperplasia or atypical lobular hyperplasia) vs. cancerous (e.g., carcinoma in situ such as ductal carcinoma in situ (DCIS) and/or lobular carcinoma in situ (LCIS)) vs. invasive (e.g. carcinomas such as invasive ductal carcinoma and/or invasive lobular carcinoma). The signature profiles are identified based upon multiple sampling of reference breast tissue samples from independent cases of breast cancer and provide a reliable set of mol. criteria for identification of cells as being in one or more particular stages and/or grades of breast cancer. The gene CRIP1 is especially prominent and thus may be a potential biomarker for the detection of breast cancer including the pre-malignant stage of atypical ductal hyperplasia. The epithelium-specific transcription factor ELF5 is also noteworthy since it maps to chromosome 11p13-15, a region subject to frequent loss of heterzygosity and rearrangement in multiple carcinoma including breast cancer.

L10 ANSWER 15 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:409169 HCAPLUS
DOCUMENT NUMBER: 138:380506
TITLE: Genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses
INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine
PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003038130	A2	20030508	WO 2002-US34888	20021031
WO 2003038130	A3	20040212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-335048P P 20011031
US 2001-335183P P 20011102
WO 2002-US34888 A 20021031

AB The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 16 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:320041 HCAPLUS
DOCUMENT NUMBER: 138:335903
TITLE: Identification of genes **expressed** in skeletal muscle associated with abnormal glucose tolerance for diagnosis of type 2 diabetes mellitus using microarrays
INVENTOR(S): Lindgren, Cecilia M.; Hirschhorn, Joel N.; Tamayo, Pablo; Daly, Mark J.; Lander, Eric S.; Altshuler, David M.
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA; The General Hospital Corporation; University of Lund
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033676	A2	20030424	WO 2002-US33524	20021017

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-330147P P 20011017

AB The present invention features method for identifying an individual having impaired glucose tolerance, impaired glucose homeostasis and/or type 2 diabetes mellitus according to gene **expression** profiles of informative genes. The present invention also features methods of identifying a compound that modulates impaired glucose tolerance, impaired glucose homeostasis and/or type 2 diabetes mellitus, as well oligonucleotide microarrays having immobilized thereon one or more probes

for one or more informative genes.

L10 ANSWER 17 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:97550 HCAPLUS
DOCUMENT NUMBER: 138:164674
TITLE: Molecular markers for hepatocellular carcinoma and their use in diagnosis and therapy
INVENTOR(S): Debuschewitz, Sabine; Jobst, Juergen; Kaiser, Stephan
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010336	A2	20030206	WO 2002-EP8305	20020725
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10136273	A1	20030213	DE 2001-10136273	20010725
WO 2004011945	A2	20040205	WO 2003-EP8243	20030725
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: DE 2001-10136273 A 20010725
WO 2002-EP8305 A 20020725

AB The invention relates to mol. markers occurring for hepatocellular carcinoma. The invention more particularly comprises gene sequences or peptides coded thereby which can be regulated upwards or downwards for hepatic cell carcinoma (HCC) in relation to healthy, normal liver cells in the **expression** thereof. The invention also relates to the use of said sequences in the diagnosis and/or therapy of HCC and for screening purposes in order to identify novel active ingredients for HCC. The invention also relates to an HCC specific cluster as a unique diagnostic agent for HCC.

L10 ANSWER 18 OF 93 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003591848 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14506264
TITLE: Myosin phosphatase-Rho interacting protein. A new member of the myosin phosphatase complex that directly binds RhoA.
AUTHOR: Surks Howard K; Richards Christopher T; Mendelsohn Michael E
CORPORATE SOURCE: Molecular Cardiology Research Institute, Cardiology Division and Department of Medicine, Tufts-New England

Medical Center, Boston, Massachusetts 02111, USA..
Hsurks@tufts-nemc.edu
CONTRACT NUMBER: HL55309 (NHLBI)
SOURCE: Journal of biological chemistry, (2003 Dec 19) 278 (51) 51484-93.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040131
Entered Medline: 20040130

AB Regulation of vascular smooth muscle cell contractile state is critical for the maintenance of blood vessel tone. Abnormal vascular smooth muscle cell contractility plays an important role in the pathogenesis of hypertension, blood vessel spasm, and atherosclerosis. Myosin phosphatase, the key enzyme controlling **myosin light chain** dephosphorylation, regulates smooth muscle cell contraction. Vasoconstrictor and vasodilator pathways inhibit and activate myosin phosphatase, respectively. G-protein-coupled receptor agonists can inhibit myosin phosphatase and cause smooth muscle cell contraction by activating RhoA/Rho **kinase**, whereas NO/cGMP can activate myosin phosphatase and cause smooth muscle cell relaxation by activation of cGMP-dependent protein **kinase**. We have used yeast two-hybrid screening to identify a 116-kDa **human** protein that interacts with both myosin phosphatase and RhoA. This myosin phosphatase-RhoA interacting protein, or M-RIP, is highly **homologous** to murine p116RIP3, is **expressed** in vascular smooth muscle, and is localized to actin myofilaments. M-RIP binds directly to the myosin binding subunit of myosin phosphatase in vivo in vascular smooth muscle cells by an interaction between coiled-coil and leucine zipper domains in the two proteins. An adjacent domain of M-RIP directly binds RhoA in a nucleotide-independent manner. M-RIP copurifies with RhoA and Rho **kinase**, colocalizes on actin stress fibers with RhoA and MBS, and is associated with Rho **kinase** activity in vascular smooth muscle cells. M-RIP can assemble a complex containing both RhoA and MBS, suggesting that M-RIP may play a role in myosin phosphatase regulation by RhoA.

L10 ANSWER 19 OF 93 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003144455 EMBASE
TITLE: Novel in vitro and in vivo phosphorylation sites on protein phosphatase 1 inhibitor CPI-17.
AUTHOR: Dubois T.; Howell S.; Zemlickova E.; Learmonth M.; Cronshaw A.; Aitken A.
CORPORATE SOURCE: A. Aitken, Inst. Curie - Sect. Recherche, CNRS UMR 144, 26 rue d'Ulm, 75 248 Paris Cedex 05, United Kingdom.
alastair.aitken@ed.ac.uk
SOURCE: Biochemical and Biophysical Research Communications, (10 Jan 2003) 302/2 (186-192).
Refs: 26
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB CPI-17 is a protein phosphatase 1 (PP1) inhibitor that has been shown to act on the **myosin light chain** phosphatase.
CPI-17 is phosphorylated on Thr-38 in vivo, thus enhancing its ability to

inhibit PP1. Thr-38 has been shown to be the target of several protein **kinases** in vitro. Originally, the **expression** of CPI-17 was proposed to be smooth muscle specific. However, it has recently been found in platelets and we show in this report that it is endogenously phosphorylated in brain on Ser-128 in a domain unique to CPI-17. Ser-128 is within a consensus phosphorylation site for protein **kinase** A (PKA) and calcium calmodulin **kinase** II. However, these two **kinases** do not phosphorylate Ser-128 in vitro but phosphorylate Ser-130 and Thr-38, respectively. The **kinase** responsible for Ser-128 phosphorylation remains to be identified. CPI-17 has strong sequence similarity with PHI-1 (which is also a phosphatase inhibitor) and LimK-2 **kinase**. The novel in vivo and in vitro phosphorylation sites (serines 128 and 130) are in a region/domain unique to CPI-17, suggesting a specific interaction domain that is regulated by phosphorylation.

L10 ANSWER 20 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:505805 HCAPLUS
DOCUMENT NUMBER: 139:289617
TITLE: EphA4-Mediated Rho Activation via Vsm-RhoGEF **Expressed** Specifically in Vascular Smooth Muscle Cells
AUTHOR(S): Ogita, Hisakazu; Kunimoto, Satoshi; Kamioka, Yuji; Sawa, Hirofumi; Masuda, Michitaka; Mochizuki, Naoki
CORPORATE SOURCE: Department of Structural Analysis, National Cardiovascular Center Research Institute, Suita, Osaka, Japan
SOURCE: Circulation Research (2003), 93(1), 23-31
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rho-**kinase**, an effector of Rho GTPase, increases the contractility of vascular smooth muscle by phosphorylating **myosin light chain** (MLC) and by inactivating MLC phosphatase. A wide variety of extracellular stimuli activate RhoA via G protein-coupled receptors. In the present study, we demonstrate a novel cell-cell interaction-mediated Rho activation signaling pathway in vascular smooth muscle cells (VSMCs). Among many receptor tyrosine **kinases**, the Eph family receptors are unique in that they require cell-cell interaction to engage their ligands, ephrin. We found that a novel VSMC-specific guanine nucleotide exchange factor (GEF) for Rho (Vsm-RhoGEF/KIAA0915) was **expressed** specifically in VSMCs of several organs including the heart, aorta, liver, kidney, and spleen, as examined by the immunohistochem. anal. using a specific antibody against Vsm-RhoGEF. Based on the association of Vsm-RhoGEF with EphA4 in quiescent cells, we tested whether EphA4 and Vsm-RhoGEF were **expressed** in the same tissue and further studied the mol. mechanism of Vsm-RhoGEF regulation by EphA4. Immunohistochem. anal. showed that EphA4 and Vsm-RhoGEF **expression** overlapped in VSMCs. Addnl., tyrosine phosphorylation of Vsm-RhoGEF induced by EphA4 upon ephrin-A1 stimulation enhanced the Vsm-RhoGEF activity for RhoA. The requirement of Vsm-RhoGEF for ephrin-A1-induced assembly of actin stress fibers in VSMCs was shown by the overexpression of a dominant-neg. form of VSM-RhoGEF and by the depletion of Vsm-RhoGEF using RNA interference. These results suggested that ephrin-A1-triggered EphA4-Vsm-RhoGEF-RhoA pathway is involved in the cell-cell interaction-mediated RhoA activation that regulates vascular smooth muscle contractility.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 93 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:564620 BIOSIS

DOCUMENT NUMBER: PREV200300562896
TITLE: THE CLASS III MYOSIN, WHICH LOCALIZES TO THE ACTIN FILAMENT BUNDLES AND CALYCAL PROCESSES OF ROD AND CONE PHOTORECEPTORS, HAS AN ACTIN BINDING DOMAIN IN ITS TAIL.
AUTHOR(S): Dose, A. C. [Reprint Author]; Erickson, L.; Burnside, B. [Reprint Author]
CORPORATE SOURCE: Molecular/Cellular Biology, UC Berkeley, Berkeley, CA, USA
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 4260. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003

AB Purpose: This study examines the actin-binding properties of myosin IIIA. This protein localizes specifically to the core actin filament bundles of photoreceptor calycal processes. Myo3A has an N-terminal **kinase** domain and a highly conserved motor domain, followed by neck and tail domains. The neck and tail contain nine putative calmodulin binding sites followed by two conserved domains: a apprx50 amino acid tail **homology** domain I (3THDI), seen in all class III myosins to date, and a 22 amino acid tail **homology** domain II (3THDII) specific to myosin IIIAs. Methods: We began by examining the ability of native Myo3A and a 3A-tail fusion protein to co-sediment with the detergent extracted photoreceptor cytoskeleton. We next used heterologous **expression** studies in Hela cells and actin-spindown assays to examine the actin binding properties of the Myo3A. Results: Native Myo3A co-sediments with the photoreceptor cytoskeleton, and can be released by the addition of ATP. In Hela cells, **expressed** Myo3A localizes to actin filaments and concentrates at the tips of filopodia. A point mutation critical to motor activity abolishes this filapodaial localization, as does the deletion of the C-terminal tail-tip (3THDII), the conserved domain at the extreme C-terminus. A GST fusion protein containing the C-terminal 202 amino acids of the myoIIIA tail co-sedimented with the cytoskeletal fraction of rod photoreceptors. In Hela cell transfections, GFP-tail and tail-tip (3THDII) fusion proteins localize to actin filaments, whereas the GFP-tail minus 3THDII was cytosolic. The 202-amino acid tail fusion protein (containing 3THDI and 3THDII) and a 22-amino acid tail-tip fusion protein (containing only 3THDII) both co-sedimented with F-actin, but a tail fusion protein missing the 3THDII remained in the supernatant. Within 3THDII, we identified an actin-binding motif DXRXXL, first identified as a novel actin-binding motif in **myosin light chain kinase** (**MLCK**, Smith et al., 1999). An Arg to Ala point mutation in this motif eliminated the ability of the 3THDII to localize to actin filaments in Hela cells and similarly the GFP-3THDII(R to A) did not bind to actin in sedimentation assays. Conclusion: Myo3A associates with the cytoskeleton in an ATP-dependent manner in vitro and localizes to actin filaments in vivo. Actin association is dependent on a functional motor domain and an intact actin-binding motif at the tip of the tail domain. (Supported by NIH grant EY03575)

L10 ANSWER 22 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-18305 BIOTECHDS
TITLE: New **kinase** proteins related to **myosin light chain kinase** **subfamily** and encoding polynucleotide, useful for diagnosing, treating disease or condition mediated by the **kinase** protein and for identifying modulators;

vector-mediated **recombinant** protein gene transfer and **expression** in host cell, DNA chip and DNA microarray for use in drug screening, disease diagnosis, therapy, gene therapy and pharmacogenomics

AUTHOR: WEI M; KETCHUM K; DI FRANCESCO V; BEASLEY E M
PATENT ASSIGNEE: PE CORP NY
PATENT INFO: WO 2002040683 23 May 2002
APPLICATION INFO: WO 2000-US32616 14 Nov 2000
PRIORITY INFO: US 2001-858664 17 May 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-500223 [53]

AB DERWENT ABSTRACT:

NOVELTY - An isolated **human kinase** peptide (I) consisting of or comprising a sequence (S1) of 1665 amino acids, an allelic variant or ortholog of (S1) encoded by a nucleic acid molecule (II) that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule having a sequence (S2) of 5207 base pairs as given in specification or fragment of (S1) having 10 contiguous amino acids, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (II) consisting of or comprising a nucleotide sequence (or its complement) that encodes (I), its allelic variant, ortholog or fragment; (2) an isolated antibody (III) that selectively binds to (I); (3) a gene chip comprising (II); (4) a transgenic non-**human** animal comprising (II); (5) a nucleic acid vector (IV) comprising (II); (6) a host cell (V) containing (IV); (7) producing (I); (8) detecting the presence of (I) in a sample, by contacting the sample with a detection agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide; (9) detecting the presence of (II) in a sample by contacting the sample with an oligonucleotide that hybridizes to the nucleic acid molecule under stringent conditions and determining whether the oligonucleotide binds to the nucleic acid molecule in the sample; (10) identifying a modulator of (I) comprising contacting (a cell **expressing**) (I) with an agent and determining if the agent has modulated the function or activity of (I); (11) identifying an agent that binds to (I) comprising contacting (I) with an agent and assaying the mixture to determine whether a complex is formed with the agent bound to (I); (12) a pharmaceutical composition (PC) comprising an agent identified using (I); (13) an isolated **human kinase** peptide (VI) having an amino acid sequence that shares at least 70% **homology** with (S1); and (12) an isolated nucleic acid molecule encoding a **human kinase** peptide, sharing at least 80% **homology** with (S2).

WIDER DISCLOSURE - Also disclosed are: (1) new agents identified by screening assays using (I); (2) kits comprising (III), to detect the presence of a protein in a sample; (3) kits for detecting the presence of a **kinase** nucleic acid in a biological sample; and (4) nucleic acid detection kit, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information of (II).

BIOTECHNOLOGY - Preparation: (I) is prepared by introducing (II) into a host cell, and culturing the host cell under conditions in which the peptides are **expressed** from the nucleotide sequence (claimed). Preferred Peptide: (VI) shares at lest 90% **homology** with (S1). Preferred Method: In the method for identifying a modulator of (I), the agent is administered to a host cell comprising an **expression** vector that **expresses** (I).

ACTIVITY - None given.

MECHANISM OF ACTION - Gene therapy. No supporting data is given.

USE - An agent identified using (I) is useful for treating a disease or condition mediated by a **human kinase** protein (claimed). (I) and (II) are useful as models for the development of **human** therapeutic targets, aid in the identification of

therapeutic proteins and serve as targets for the development of **human** therapeutic agents that modulate **kinase** activity in cells and tissues that **express** the **kinase**. (I) and (II) are further useful as a query sequence to perform a search against sequence databases to identify other family members or related sequences. (I) is useful to raise antibodies or elicit another immune response, as a reagent in assays designed to quantitatively determine levels of the protein in biological fluids, and as markers for tissues in which the corresponding protein is **expressed** and to identify the binding partner/ligand so as to develop a system to identify inhibitors of the binding interactions. (I) is useful in competition binding assays to discover compounds that interact with the **kinase**. The **kinase**-modulating agents are useful in an animal or other model to determine the efficacy, toxicity, mechanism of action or side effects of treatment with such an agent. The **kinase** proteins also provide a target for diagnosing a disease or predisposition to a disease mediated by the peptide, in pharmacogenomic analysis and for treating disorders characterized by an absence of inappropriate, or unwanted **expression** of the protein. (II) is useful as primers for polymerase chain reaction (PCR) to amplify any given region of a nucleic acid molecule and to synthesize antisense molecules of desired length and sequences, for constructing **recombinant** vectors, **expressing** antigenic portions of the proteins, as probes for determining the chromosomal positions of the nucleic acid molecules by in situ hybridization, making vectors containing the gene regulatory regions of the nucleic acid molecules, designing ribozymes, constructing host cells **expressing** a part, or all of (II), constructing transgenic animals, as hybridization probes for determining the presence, level, form and distribution of nucleic acid **expression**, to detect the presence of, or to determine levels of a specific nucleic acid molecule in cells, tissues, and in organisms and for drug screening to identify compounds that modulate **kinase** nucleic acid **expression**. (II) is further useful for monitoring the effectiveness of modulating compounds on the **expression** or activity of the **kinase** gene in clinical trials or in a treatment regimen, in diagnostic assays for qualitative change in **kinase** nucleic acid **expression** and for testing an individual for a genotype. (III) is useful to isolate, purify and detect the presence of (I) in cells or tissues to determine the pattern of **expression** of the protein among various tissues in an organism, to assess abnormal tissue distribution or abnormal **expression** during development or progression of a biological condition, to assess normal and aberrant subcellular localization of cells in various tissues in an organism, in pharmacogenomic analysis, for tissue typing and for inhibiting protein function. (V) is useful for producing a **kinase** protein or peptide, conducting cell-based assays involving the **kinase** protein, identifying **kinase** protein mutants and to produce non-**human** transgenic animals which are useful for studying the function of a **kinase** protein and identifying and evaluating modulators of **kinase** protein activity. (96 pages)

L10 ANSWER 23 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-12398 BIOTECHDS
TITLE: Novel polynucleotide encoding novel **human** protein sharing structural similarity with animal **kinases** e.g. serine-threonine, calcium/calmodulin-dependent, and **myosin light chain** **kinases**, useful as probes and primers; vector-mediated gene transfer, **expression** in host cell, antibody, antisense oligonucleotide and ribozyme for **recombinant** protein production, drug screening and gene therapy
AUTHOR: FRIDDLE C J; HILBUN E; NEPOMNICHY B; HU Y
PATENT ASSIGNEE: LEXICON GENETICS INC

PATENT INFO: WO 2002018555 7 Mar 2002
APPLICATION INFO: WO 2000-US26776 31 Aug 2000
PRIORITY INFO: US 2000-229280 31 Aug 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-292200 [33]
AB DERWENT ABSTRACT:
NOVELTY - An isolated novel **human** protein (NHP) encoding nucleic acid, where the NHP shares structural similarity with animal **kinases** e.g. serine-threonine, calcium/calmodulin-dependent, and **myosin light chain kinases**, is new.

DETAILED DESCRIPTION - An isolated novel **human** protein (NHP) encoding nucleic acid, where the NHP shares structural similarity with animal **kinases** e.g. serine-threonine, calcium/calmodulin-dependent, and **myosin light chain kinases**, is new. The NHP nucleic acid comprises a nucleotide sequence encoding a fully defined sequence of 683 (S2), 654 (S4), 388 (S7) and 398 (S9) amino acids as given in the specification, and which hybridizes under stringent conditions to a fully defined sequence of 2052 (S1) or 1167 (S6) nucleotides as given in specification, or its complement. An INDEPENDENT CLAIM is also included for an isolated nucleic acid molecule that comprises at least 24 contiguous bases of (S6).

WIDER DISCLOSURE - The following are disclosed: (1) novel **human** proteins (NHP) having a fully defined sequence of (S2), (S4), (S7) or (S9) encoded by NHP polynucleotides where the proteins are useful for generating antibodies, reagents in diagnostic assays, identification of other cellular gene products related to NHP, as reagents in assays for screening compounds that can be used as pharmaceutical reagents for treating mental, biological or medical disorders and diseases; (2) a nucleic acid selected from: (a) a sequence that encode mammalian **homologs** of NHP including the specifically described NHPs and the NHP gene products (b) a sequence that encode one or more portions of the NHPs that correspond to functional domains, and the polypeptide products specified by such nucleotide sequences (c) a sequence that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences (d) a sequence that encode fusion proteins containing a coding region from an NHP or one of its domains (e.g. receptor or ligand binding domain) fused to another peptide or polypeptide, or (e) therapeutic or diagnostic derivatives of the polynucleotides; (3) agonist and antagonist of NHPs; (4) compounds that modulate the **expression** or activity of NHPs and nucleotide sequences (nucleotide constructs) that can be used to inhibit the **expression** of NHP (e.g., antisense, ribozyme molecules, etc.,) or to promote the **expression** of NHP; (5) transgenic animals that **express** NHP transgene or knock-outs that do not **express** a functional NHP; (6) processes of identifying compounds that modulate i.e., act as agonist or antagonist of NHP **expression** and/or NHP activity; (7) antibodies against NHP and idiotypic antibodies against anti-NHP antibodies; (8) fusion proteins comprising NHP protein; (9) degenerate nucleic acid variants of the NHP polynucleotide sequences; (10) DNA vectors that contain any of the NHP coding sequences and/or their complements; (11) genetically engineered host cells **expressing** NHP coding sequences operatively associated with a regulatory element; (12) analogues, derivatives and NHP **homologues** from other species; (13) proteins that are functionally equivalent to NHP encoded by the above described nucleotide sequences; and (14) pharmaceutical formulations comprising the NHP polynucleotide sequences.

BIOTECHNOLOGY - Isolation: The NHP polynucleotides were complied from sequences available in GENBANK, and cDNAs generated from kidney, testis, trachea, esophagus, pituitary, **human** gene trapped products ((S2) and (S4)) or bone marrow and skeletal muscle mRNAs.

ACTIVITY - None given. No biological data is given.
MECHANISM OF ACTION - Gene therapy. No biological data is given.
USE - The NHP polynucleotide sequences that encode NHPs sharing structural similarity with animal **kinases** including NIMA (never in mitosis A) related **kinases**, serine-threonine **kinases**, calcium/calmodulin-dependent **kinases**, and **myosin light chain kinases**, when knocked out provide a method for identifying phenotypic **expression** of the particular gene as well as a method of assigning function to previously unknown genes, for identifying coding sequence and mapping a unique gene to a particular chromosome and in the identification of biologically relevant splice junctions. Complementary sequences of (I) that hybridize to (I) can be used in conjunction with PCR to screen libraries, isolate **clones** and prepare **cloning** and sequencing templates. Such oligonucleotides can also be used as hybridization probes for screening libraries, for assessing gene **expression** patterns. The probes are useful for identification, selection and validation of novel molecular targets for drug discovery. Labeled NHP nucleotide probes can be used to screen a **human** genomic library which is helpful for identifying polymorphisms, determining the genomic structure of a given locus/allele and designing diagnostic tests. The probe sequences also have use in defining and monitoring both drug action and toxicity. Oligonucleotides complementary to NHPs may encode or act as NHP antisense molecules, or may be used as part of ribozyme and/or triple helix sequences. Addressable arrays comprising the NHP polynucleotides can be used to identify and characterize the temporal and tissue **expression** of a gene. The use of addressable arrays comprising the NHP polynucleotide sequence provide detailed information about transcriptional changes involved in specific pathway, potentially leading to the identification of novel components or gene functions that manifest themselves as novel phenotypes. Microarray formats comprising NHP polynucleotide sequences can be used to screen collections of genetic material from patients who have a particular medical condition. The sequences are also useful for identifying mutations associated with a particular disease and also as a prognostic or diagnostic assay. (I) is also useful in the molecular mutagenesis/evolution of proteins that are at least partially encoded by the described novel sequences.
EXAMPLE - None given. (46 pages)

L10 ANSWER 24 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-13580 BIOTECHDS
TITLE: New isolated cardiac **myosin light chain kinase** (cMLCK) protein, useful for identifying cMLCK modulators that are used for treating cardiac dysfunction e.g. systolic or diastolic dysfunction, myocardial infarction;
vector-mediated **recombinant** protein gene transfer and **expression** in host cell, transgenic animal model construction, antisense, DNA primer, DNA probe, polymerase chain reaction and monoclonal antibody for use in drug screening and cardiovascular disease therapy and gene therapy
AUTHOR: EPSTEIN N D; HASSANZADEH S; WINITSKY S; DAVIS J S
PATENT ASSIGNEE: US DEPT HEALTH and HUMAN SERVICES
PATENT INFO: WO 2002024889 28 Mar 2002
APPLICATION INFO: WO 2000-US28639 12 Sep 2000
PRIORITY INFO: US 2000-232456 13 Sep 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-394135 [42]
AB DERWENT ABSTRACT:
NOVELTY - An isolated cardiac **myosin light chain kinase** (cMLCK) protein (I) comprising a fully defined sequence of 596 amino acids (S2) as given in specification, amino

acid sequences differing from (S2) by one or more conservative amino acid substitutions and having biological activity of cMLCK, or amino acid sequences having 70% identity to above mentioned sequences and having biological activity of cMLCK, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (II) encoding (I); (2) a **recombinant** nucleic acid molecule (III) comprising a promoter sequence operably linked to (II); (3) a **recombinant** vector (IV) comprising (III); (4) a cell (V) transformed with (IV); (5) a cell (VI) transformed with (III) which comprises (II) in antisense orientation relative to promoter sequence; (6) a transgenic non-**human** animal (VII) comprising (III); (7) a transgenic non-**human** animal (VIII) comprising (III) which comprises (II) in antisense orientation relative to the promoter sequence;(8) an isolated oligonucleotide (IX) of at least 10 nucleotides in length that specifically hybridizes under stringent conditions to (II);(9) modifying (M1) a level of **expression** of cMLCK in a cell of an animal involves **expressing** in a cell a **recombinant** genetic construct comprising a promoter operably linked to a nucleic acid molecule comprising (IX), thereby modifying the **expression** of the cMLCK; (10) a specific binding agent (X) that specifically binds (I); (11) enhancing or preserving (M2) cardiac function in a subject which involves modulating a stretch activation in a myocardial cell of the subject; and (12) a kit (XI) for detecting cMLCK nucleic acid sequence comprising a container containing an oligonucleotide primer having a sequence comprising at least 10 contiguous nucleotides of (S1).

WIDER DISCLOSURE - The following are disclosed: (1) nucleic acid sequence complementary to (II); (2) **human** cMLCK genomic structure and sequence; and (3) nucleotide and amino acid sequence variants of cMLCK.

BIOTECHNOLOGY - Preferred Nucleic Acid: (II) has a fully defined sequence of 1791 nucleotides (S1) as given in specification, the nucleic acid sequence having at least 80% identity with (S1), or a nucleic acid sequence which hybridizes under stringent conditions to (S1), where the nucleic acid molecule hybridizes to (S1) under conditions in which DNA molecules with more than 25% mismatch will not hybridize to each other. (III) preferably is in antisense orientation relative to the promoter sequence. Preferred Transgenic Animal: In (VII), the cMLCK is overexpressed, and in (VIII) the cMLCK is underexpressed. Preferred Oligonucleotide: (IX) preferably comprises 10 (preferably 20) contiguous nucleotides of (S1). Preferred Method: In (M1), preferably the nucleic acid molecule is in antisense orientation relative to the promoter. In (M2), modulating stretch activation involves modulating myosin phosphorylation or activity of cMLCK in a myocardial cell of the subject. Modulating activity of cMLCK involves: (a) administering to the subject a compound that modulates cMLCK activity; and (b) delivering to the subject's heart, a vector comprising a transgene encoding a peptide having cMLCK biological activity, or a peptide which inhibits cMLCK activity. The transgene encoding peptide comprises at least 20 contiguous nucleotides of (S1), and the vector comprising this transgene is delivered to one or more regions of the heart such as papillary muscle, left ventricle myocardial free wall, septum, right ventricular myocardial free wall, apical myocardium, basal myocardium, and atrial myocardium.Preferred Binding Agent: (X) is a polyclonal or monoclonal antibody, and specifically binds a polypeptide comprising a sequence of Gly-Ala-Asn-Ser-Asn-Val-Phe-Gly-Ala-Asn-Ser-Asn-Val-Phe. Preferred Kit: The kit preferably comprises a pair of oligonucleotide primers each having a sequence comprising at least 20 contiguous nucleotides of (S1).

ACTIVITY - Cardiant.

MECHANISM OF ACTION - Cardiac stretch activation modulator by modulating myosin phosphorylation or cMLCK biological activity in myocardial cells of subject; Gene therapy; cMLCK modulators. No supporting data is given.

USE - (I) is useful for detecting enhanced susceptibility of a

subject to cardiac dysfunction which involves detecting altered **expression** of (I) (i.e., an increased or decreased **expression** of cMLCK as compared to a control) or detecting **expression** of mutant cMLCK in a sample (e.g., sample of cardiac myocytes or cardiac fibers) obtained from the subject. The method further involves evaluating functional characteristic of cardiac fibers. (I) is useful for screening for an agent that modulates cMLCK biological activity which involves incubating the agent at a first concentration with (I) and a polypeptide that is phosphorylated by (I) under conditions that permit phosphorylation of the polypeptide by cMLCK and detecting phosphorylation of the polypeptide. The method further involves incubating the agent at a second concentration with (I) and repeating the steps as described above. The phosphorylation of the polypeptide obtained after incubation with first concentration of the agent is compared with phosphorylation obtained after incubation with the second concentration of the agent thereby determining if the agent modulates cMLCK biological activity. The phosphorylation of the polypeptide is detected by immobilizing the polypeptide, contacting the immobilized polypeptide with a primary specific binding agent that specifically binds to a phosphorylated form of the polypeptide, removing primary specific binding agent not specifically bound to the immobilized polypeptide and detecting the presence of primary specific binding agent bound to the immobilized polypeptide. Detecting primary specific binding agent which is bound to the immobilized peptide involves contacting the specific binding agent with the secondary binding agent which comprises a detectable label, removing the any secondary specific binding agent not specifically bound to the primary specific binding agent, and detecting the presence of secondary specific binding agent bound to the primary specific binding agent. The method further involves providing a source of labeled ATP and detecting phosphorylation of the polypeptide by detecting label from the labeled ATP incorporated into the polypeptide. (II) is useful for detecting enhanced susceptibility of a subject to cardiac dysfunction which involves detecting presence of a mutation, a duplication, or a deletion of (II) in a sample obtained from the subject, where the cardiac dysfunction is a result of cardiac hypertrophy or hypertrophic cardiomyopathy. (M2) is useful for enhancing or preserving cardiac function in a subject having cardiac dysfunction, and harboring a mutation in cMLCK allele. The method is useful for enhancing or preserving cardiac function in a subject having cardiac dysfunction such as systolic dysfunction, diastolic dysfunction, cardiac hypertrophy, cardiomyopathy, coronary heart disease, myocardial infarction, or congestive heart failure, or for preserving cardiac function, or cardiac dysfunction which comprises valvular heart disease such as mitral valve disease, tricuspid valve disease, mitral insufficiency, tricuspid insufficiency, or mitral valve prolapse. (IX) is useful as hybridization probes or PCR primers for detecting presence of cMLCK nucleic acid sequence having a sequence of (S1) or having 80% sequence identity with (S1) in a biological specimen. The oligonucleotide primer preferably comprises at least 10 contiguous nucleotides of (S1) or a sequence having 80% sequence identity with (S1) (all claimed). (II) is useful for producing animals having increased levels of cMLCK protein, as well as in diagnostic methods to detect defects or alterations in cMLCK **expression** or cMLCK protein production. (M2) is useful for treating cardiac dysfunction, e.g., systolic or diastolic dysfunction, cardiac hypertrophy, cardiomyopathy, coronary heart disease, myocardial infarction, or congestive heart failure. Compounds identified as cMLCK modulators using (I) are useful for treating cardiac dysfunction as described above.

ADMINISTRATION - The cMLCK modulators are administered by oral, intravaginal, rectal, parenteral route, etc. No specific clinical dosages are given.

EXAMPLE - Published rabbit skeletal muscle **myosin light chain kinase** (**MLCK**) cDNA sequence was used to design a set of primer pairs to amplify unique

fragments from both rabbit skeletal muscle and cardiac RNA. A product from one pair of primers TGATCCAGCTGTACGCAGCC-3', 5'-CTTGAGGTCCAGGTGCAGC-3' yielded identically sized 201 base pair (bp) fragments from both templates. Subcloning and sequencing showed identical sequences suggesting that either skeletal muscle **MLCK** or a partially **homologous** isoform could be found in rabbit cardiac muscle. A possible genomic contamination was excluded since the same primers crossed an intron-exon boundary and generated a greater than 500 bp size fragment from rabbit genomic DNA. The divergence of the latter genomic sequence from the cDNA sequence marked what was later found to be the **homologue** of the **human** intron-exon-6 boundary.
Human genomic DNA was used as a template from which a **MLCK** fragment was amplified using primers derived from the rabbit sequence. In order to avoid cross-reaction with **human** smooth muscle **MLCK** sequence, the DNA sequence flanking the **homologous** intron-6 insertion point of rabbit skeletal and smooth muscle **MLCK** was compared. A downstream region of amino acid divergence was identified in the presumed region of skeletal **MLCK** exon 7. The nucleotide sequence encoding this stretch was then compared for differences between rabbit and rat skeletal muscle **MLCK** cDNA sequence. A degenerate primer was prepared that encoded both rat and rabbit sequence as well as some possible third position codon changes. (5'-AGGTCCAg/aGTGCAGc/a/t/gACCCg/tCA-3' upstream primers in presumed **human** exon 6 that were divergent between rabbit smooth and skeletal muscle **MLCK** were conserved between rat and rabbit skeletal **MLCK** sequence. Thus, minimal changes from the rabbit upstream primer sequence were made (5'-CGTg/cCTGTTCATGGAGT-3'). Using the latter 2 primers, the fragment obtained from **human** genomic DNA contained an 82 bp intron. Subcloning and sequencing yielded coding sequence, which internal to the primer ends, showed significant **homology** at the amino acid level to rabbit skeletal muscle **MLCK**. In order to obtain a full length **clone** from **human** cardiac RNA, 5' and 3' rapid amplification of cDNA ends (RACE) was performed using the Marathon RACE kit. The exon 6 sequence obtained from **human** DNA was used to generate 2 primers for 5' and 3' RACE. The 5' RACE fragment was denatured and annealed to the **human** exon 6 containing fragment. Polymerase chain reaction (PCR) amplification using primers from the 5' ends of both fragments were used to join both fragments. A similar process was then used to join this fragment with the 3' RACE product to produce a full length cDNA fragment. This full length cDNA was sequenced and matched the sequence of reverse transcriptase (RT-PCR) amplified product from **human** skeletal muscle. The full-length cDNA for cMLCK was 1791 base pairs long, and encoded a protein of 596 amino acids. In order to obtain full length genomic sequence, a primer based in **human** intron 6 (5'-CCACGGCTTGCTCCGTGCCT-3') was used together with an upstream exon 6 primer (5'-ATCGAGACTCCGCATGAGAT-3') to screen a **human** P1 library. Intron-exon boundaries were established by amplifying the intervening introns using cDNA sequence derived primers as well as direct sequencing of the P1 **clone**. Sequence of the coding portions of the genomic **clone** matched the full length cDNA sequence obtained through RACE. There was significant **homology** between the predicted amino acid translation of the **human** cMLCK sequence and rabbit skeletal muscle **MLCK** sequence. However, amino acid sequence divergence was substantial in the amino-terminal end. The genomic DNA of **human** cMLCK comprises 12 exons. (105 pages)

L10 ANSWER 25 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-12234 BIOTECHDS
TITLE: Novel muscle ring finger protein useful for drug screening, and for diagnosing and treating diseases, particularly cardiomyopathies;
vector-mediated sense or antisense gene transfer, **expression** in host cell and monoclonal antibody

preparation by hybridoma cell culture for **recombinant** protein production, drug screening and genetherapy

AUTHOR: OLSON E N; SPENCER J A
PATENT ASSIGNEE: UNIV TEXAS SYSTEM
PATENT INFO: WO 2002006318 24 Jan 2002
APPLICATION INFO: WO 2000-US22896 18 Jul 2000
PRIORITY INFO: US 2000-219020 18 Jul 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-241506 [29]

AB DERWENT ABSTRACT:

NOVELTY - A purified muscle ring finger (MURF) protein (I), selected from MURF-1, MURF-2 and MURF-3 comprising a 366, 545 and 343 residue amino acid sequence (S1), respectively, all given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a DNA segment (II) encoding (I); (2) a host cell (III) comprising (II) which comprises a promoter heterologous to MURF-1, MURF-2 or MURF-3 coding region; (3) use of a host cell comprising an **expression** cassette comprising a polynucleotide encoding (I) and a promoter active in host cell, where the promoter directs the **expression** of the polypeptide, for culturing the host cell under conditions suitable for the **expression** of the MURF-1, MURF-2 or MURF-3 polypeptide; (4) an isolated nucleic acid segment (IIa) comprising at least 15 contiguous nucleotides of a 1448, 2590 or 1597 nucleotide sequence (S2), given in the specification; (5) an isolated nucleic acid segment (IIb) from 14-888 nucleotides in length that hybridizes to S2, under standard hybridization conditions; (6) a nucleic acid detection kit (K1) comprising, in suitable container means, an isolated nucleic acid segment that hybridizes under high stringency conditions to S2 or its complements; (7) a composition (C) comprising a purified MURF-1 or MURF-2 protein or peptide comprising S1; (8) a **recombinant** MURF-1, MURF-2 or MURF-3 protein or peptide prepared by **expressing** a DNA segment encoding (I) in a **recombinant** host cell and purifying the **expressed** polypeptide away from total **recombinant** host cell components; (9) an isolated peptide (Ia) of 10-50 amino acids in length, comprising S1; (10) an antibody composition (AbC) that binds to a protein or peptide including an epitope from S1; (11) a hybridoma cell that produces a monoclonal antibody that binds immunologically to (I); (12) an immunodetection kit (K2) comprising a first antibody that binds (I); (13) detecting alterations in functions of (I) in a cell; (14) increasing the activity of (I) in a cell; (15) screening a candidate substance for an effect on levels or **expression** of (I), or on MURF-directed glutamic acid modification of microtubules; (16) a transgenic non-**human** mammal, comprising a nucleic acid segment encoding (I) integrated into their genome, under the control of a heterologous promoter; (17) modulating the activity of (I) in a cell; (18) blocking or increasing the **expression** of (I) in a cell; and (19) treating (M5) cardiac failure, by increasing the activity of (I) in a cardiac cell, where the increased activity of (I) stabilizes microtubules and/or intermediate filaments.

BIOTECHNOLOGY - Isolation: (I) is isolated and purified by standard isolation and purification techniques. Preferred Sequence: (II) is a murine DNA segment positioned under the control of a promoter which is not a native coding region for (I). The coding region is positioned in reverse orientation to the promoter, so that it is capable of **expressing** an antisense product. The promoter is a **myosin light chain**-2 promoter, alpha actin promoter, troponin 1 promoter, Na+/Ca2+ exchanger promoter, dystrophin promoter, creatine **kinase** promoter, alpha7 integrin promoter, brain natriuretic peptide promoter, alpha B-crystallin/small heat shock protein promoter, alpha myosin heavy chain promoter and ANF promoter. (II) further comprises a polyadenylation signal and an origin of replication. (IIa) is 15, preferably 50 nucleotides in length. (IIb) is a viral vector selected

from retrovirus, adenovirus, herpesvirus, vacciniavirus, poxvirus and adeno-associated virus, and comprises an origin of replication. The nucleic acid is packaged in a viral particle or liposome. Preferred Protein: (Ia) is 10, preferably 50 amino acids in length. AbC comprises monoclonal antibodies that are operatively attached to a detectable label e.g. fluorescent label, chemiluminescent label, electroluminescent label, radiolabel or an enzyme. Preferred Kit: K1 further comprises a detection reagent that is a detectable label linked to the nucleic acid segment, and a pair of primers for amplifying (II). K2 further comprises a second antibody that has binding affinity for the first antibody. Both antibodies comprise a detectable label. The first antibody is bound to a solid support. Preferred Method: In M5, the activity of (I) is increased by contacting the cardiac cell with an **expression** cassette comprising (II) and a promoter active in a cardiac cell.

ACTIVITY - Cardiant.

MECHANISM OF ACTION - Modulator of (I) (claimed). No biological data is given.

USE - (I) is useful for screening a candidate substance for MURF protein-binding activity, in a cell, cell-free system or in vivo, and its effect on interaction of (I) with microtubules, homodimerization of (I), MURF-1, MURF-2 or MURF-3 stabilization of microtubules, interaction of (I) with intermediate filaments, e.g. desmin, vimentin and cytokeratin, and heterodimerization of (I). (All claimed). The screened compounds are useful for treating and preventing cardiac hypertrophy and heart diseases. (I) is useful as antigens to immunize animals for the production of antibodies.

ADMINISTRATION - (C) is administered through oral, nasal, buccal, rectal, vaginal, orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous or topical route. No dosage is suggested.

EXAMPLE - In a two-hybrid screen for cardiac factors that interact with serum response factor (SRF), a cDNA encoding a novel muscle-specific RING-finger protein, named MURF-1 was identified. Database searches with the amino acid sequence of MURF-1 revealed highest **homology** to the Opitz-G/BBB syndrome protein Mid1 and the related factor Mid2 with greatest **homology** in the RING-finger and B-box domains. Interestingly, MURF-1 did not contain the first B-box of Mid1 and Mid2 nor the butyrophilin-like domain at the C-termini of Mid2 and Mid2, suggesting functional differences between the proteins. The **expression** pattern of MURF-1 was examined during mouse embryogenesis by in situ hybridization. At E8.5 MURF-1 **expression** was observed only in the developing cardiac region and at E10.5 **expression** was restricted exclusively to the heart and the myotome of the somites which give rise to skeletal muscle. This muscle-specific **expression** continued throughout prenatal development, with **expression** observed in the heart and skeletal muscle of the intercostals, diaphragm, limbs, face and head. In adult mice, Northern analysis showed a single MURF-1 transcript of 1.5 kbase in cardiac and skeletal muscle. Extended exposures (greater than 6 days) revealed a very low level of **expression** in the lung and brain. Consistent with the restricted **expression** of MURF-1 mRNA, Western blot analysis of protein from mouse heart, quadriceps, spleen and lung, using anti-MURF antibody, detected MURF-1 protein only in heart and skeletal muscle. The size of the protein, 41 kDa, was in agreement with the size predicted from the open reading frame. (134 pages)

L10 ANSWER 26 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-11632 BIOTECHDS
TITLE: Novel isolated polynucleotide encoding **human** or murine myocardin 1 polypeptide, useful for modulating phenotype of non-cardiomyocyte cell e.g., fibroblast, to include phenotypic functions of cardiomyocyte cell; vector-mediated gene transfer to host cell for heart disease therapy and gene therapy
AUTHOR: OLSON E N; WANG D

PATENT ASSIGNEE: OLSON E N; WANG D
PATENT INFO: US 2002164735 7 Nov 2002
APPLICATION INFO: US 2001-29217 21 Dec 2001
PRIORITY INFO: US 2001-29217 21 Dec 2001; US 2000-257761 21 Dec 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-247258 [24]

AB DERWENT ABSTRACT:

NOVELTY - An isolated polynucleotide (I) encoding myocardin polypeptide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a myocardin peptide (II) of 8-50 residues comprising at least 8 consecutive residues of a fully defined murine myocardin 1 polypeptide sequence (S1) of 807 or 935 amino acids, or of a fully defined **human** myocardin 1 polypeptide sequence (S2) of 807 or 938 amino acids. All sequences are as given in the specification; (2) an isolated nucleic acid segment (III) comprising at least 15 contiguous nucleotides of a fully defined sequence (S3) of 4959, 2424, 3063 or 4960 nucleotides, as given in the specification; (3) an **expression** cassette (IV) comprising (I) operably linked to a regulatory sequence; (4) a transformed host cell (V) comprising (I), and a promoter heterologous to the polypeptide coding region, where the promoter directs **expression** of the myocardin polypeptide; (5) a fusion protein (VI) comprising myocardin protein or (II) fused to a second protein or peptide; (6) stimulating (M1) cardiac tissue regeneration, involves inhibiting the function of myocardin in a post-mitotic cardiomyocyte; (7) preparation of myocardin polypeptide by introducing into the host cells (IV) under control of a promoter operable in the host cell; (8) a monoclonal antibody (VII) that binds immunologically to polypeptide comprising (S1) or (S2) or its antigenic fragment; (9) a polyclonal antisera, antibodies of which bind immunologically to polypeptide comprising (S1) or (S2) or its antigenic fragment; (10) a hybridoma cell that produces (VII); (11) a non-**human** transgenic animal (VIII) comprising an **expression** cassette which comprises polynucleotide encoding myocardin protein or peptide, and a promoter operable in eukaryotic cells, the promoter being heterologous to the myocardin peptide or protein encoding region; (12) a non-**human** transgenic animal (IX) comprising a defective germ-line myocardin allele; (13) treating (M2) a heart disease, including cardiomyopathy, involves administering to an animal suffering from the disease an **expression** cassette comprising polynucleotide encoding myocardin protein or peptide, and a promoter operable in eukaryotic cells; (14) treating heart disease including cardiomyopathy, providing to the animal a myocardin antisense nucleic acid; (15) decreasing mortality or morbidity in a subject with heart failure by inhibiting the function of myocardin in post-mitotic cardiomyocytes in the subject, or by increasing the level of myocardin in fibroblasts to generate cardiomyocytes in the subject; (16) screening (M3) for a candidate substance for an effect on myocardin regulation of cardiomyocyte development, involves providing myocardin and GATA (a cardiac transcription factor) to a cell, admixing myocardin and GATA in the presence of the candidate substance, and measuring the effect of the candidate substance on the **expression** of a cardiac lineage marker, where a difference in the **expression** of the cardiac lineage marker, as compared to an untreated cell, indicates that the candidate substance effects myocardin regulation of cardiomyocyte development; (17) screening (M4) for a modulator of myocardin **expression**, involves providing a cell that **expresses** a myocardin polypeptide, contacting the myocardin polypeptide with a candidate substance, and measuring the **expression** of myocardin, where a difference in myocardin **expression**, indicates that the candidate substance is a modulator of myocardin **expression**; (18) screening (M5) a candidate substance for myocardin binding activity, involves providing a myocardin polypeptide, contacting myocardin polypeptide with the candidate

substance, and determining the binding of the candidate substance to the myocardin polypeptide; (19) a method (M6) for modulating the phenotype of a non-cardiomyocyte cell (e.g., fibroblast) to include one or more phenotypic functions of a cardiomyocyte cell, which involves introducing (IV) into the non-cardiac cell, where the promoter directs the **expression** of the polypeptide; and (20) a method (M7) for generating a cardiomyocyte which involves introducing into a cardiac fibroblast (IV) comprising (I) and a promoter active in the fibroblast, where the promoter directs the **expression** of the polypeptide.

WIDER DISCLOSURE - The following are disclosed: (1) myocardin polypeptide having a sequence of (S1) or (S2); (2) a polynucleotide sequence encoding (II); (3) sequences that are degenerate with respect to (I); (4) DNA segments that are complementary to (I); (5) variants of myocardin polypeptide; and (6) making (VIII) or (IX).

BIOTECHNOLOGY - Preferred Peptide: (II) preferably comprises 12 consecutive residues of (S1) or (S2). Preferred Polynucleotide: (I) further comprises a promoter operable in eukaryotic cells. (III) is 15, preferably 2000 nucleotides in length, and comprises at least 20, preferably 50 contiguous nucleotides of (S3). Preferred Cassette: In (IV), the regulatory sequence comprises a promoter heterologous to the coding sequence. The promoter is a tissue specific promoter, or muscle specific promoter such as **myosin light chain** -2 promoter, alpha actin promoter, troponin 1 promoter, Na+/Ca2+ exchanger promoter, dystrophin promoter, creatine **kinase** promoter, alpha7-integrin promoter, brain natriuretic peptide promoter, alpha B-crystalline/small heat shock protein promoter, alpha myosin heavy chain promoter or atrial natriuretic factor (ANF) promoter. Preferably, (IV) comprises a cardiac muscle specific promoter (e.g., alpha-myosin heavy chain or ANF promoter). (IV) is contained in a gene delivery vector e.g., viral vector such as retroviral vector, adenoviral vector, adeno-associated viral vector, vaccinia viral vector, herpes viral vector, polyoma viral construct or Sindbis viral vector. (IV) further comprises a polyadenylation signal, and a second polynucleotide encoding a second polypeptide e.g., cardiac transcription factor. Preferred Method: The function of myocardin is inhibited by providing to the post-mitotic cardiomyocyte an antisense nucleic acid that inhibits transcription or translation of a myocardin mRNA. Preferably, the method involves introducing into the post-mitotic cardiomyocyte an **expression** cassette encoding myocardin antisense RNA and a promoter active in the cardiomyocytes. In (M2), the **expression** cassette is comprised within a replication defective **expression** vector, e.g., viral vector, and comprises a cardiac specific promoter. In (M3), the effect of the candidate substance on **expression** of cardiac lineage marker (preferably Nkx2.5) is measured by RNA hybridization, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), immunologic detection of myocardin, enzyme linked immunosorbent assay (ELISA), immunohistochemistry. The myocardin and GATA are provided to a cell located in an animal e.g., fibroblast, cardiomyocyte. The modulator identified by the method increases or decreases the **expression** of the cardiac lineage marker. In (M4), the modulator enhances or inhibits myocardin **expression**. The candidate modulator is a pharmaceutical composition. (M5) is carried out in a cell, cell free system or in vivo. The candidate substance is an inhibitor or enhancer of myocardin. M6 further comprises measuring cardiac lineage markers, by RNA hybridization, polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR) or Western analysis. The **expression** cassette further comprises a second polynucleotide encoding a cardiac transcription factor (e.g., GATA4). The second polynucleotide is under the control of a second promoter. Optionally, the first and second polynucleotides are under the control of the same promoter. M6 further comprises introducing a second **expression** cassette into the non-cardiomyocyte cells, where the second **expression** cassette comprises a polynucleotide encoding a second polypeptide and a second promoter active in the

non-cardiomyocyte cells, where the second promoter directs the **expression** of the second polypeptide. In M7, the **expression** vector comprises lipid-based vector or a viral vector. Preferred Transgenic Animal: (VIII) is a mouse. (IX) comprises two defective germ-line myocardin alleles.

ACTIVITY - Hypotensive; Cardiant.

MECHANISM OF ACTION - Gene therapy; Antisense therapy; Reprograms cardiac fibroblasts to cardiomyocytes; Inducer of cardiomyocyte development; Inducer of hypertrophy in cardiomyocytes. The effects of myocardin in growth and/or all differentiation of cardiomyocytes was assessed by overexpressing myocardin in cardiomyocytes using adenoviral delivering system. Cardiomyocyte cultures were prepared by dissociation of 1-day-old neonatal rat hearts and were plated differentially to remove fibroblasts. Cells were plated on glass coverslips coated with 4 micrograms/cm2 laminin in 4:1 Dulbecco's modified Eagle's medium (DMEM):199 medium with 10% horse serum and 5% fetal calf serum at a density of 5 x 10 (to the power of 4) cells/cm2. Eighteen hours after plating, cells were changed into serum-free media and infected with adenoviruses **expressing** either myocardin or beta-galactosidase. For immunofluorescence, cells were fixed in 3.7% formaldehyde on ice for 30 min, permeabilized with 0.1% Triton X-100 in phosphate-buffered saline (PBS) and blocked with 5% serum in PBS for 1 hour at room temperature. Cells were incubated with monoclonal anti-alpha-actinin (sarcomeric) or anti-ANF (atrial natriuretic factor) antibodies at a dilution of 1:200 in blocking buffer for 1 hour at 37 degrees Centigrade, washed and incubated with fluorescein-conjugated horse anti-mouse IgG antibody. Following secondary antibody incubation, cells were washed with PBS. The results showed that overexpression of myocardin in neonatal cardiomyocytes induced assembly of sarcomeres and **expression** of ANF, markers of cardiac hypertrophy.

USE - (IV) is useful for modulating the phenotype of a non-cardiomyocyte cell (e.g., fibroblast) to include one or more phenotypic functions of a cardiomyocyte cell. (IV) is useful for generating a cardiomyocyte which involves introducing into a cardiac fibroblast (IV) comprising (I) and a promoter active in the fibroblast, where the promoter directs the **expression** of the polypeptide. (IV) further comprises a second polynucleotide encoding GATA4, under the control of a second promoter active in a cardiac fibroblast. The **expression** cassette further comprises a polyadenylation site and an immunological marker. (M2) is useful for treating a heart disease, including cardiomyopathy, such as myocardial infarction or hypertension (all claimed).

ADMINISTRATION - Viral vectors comprising (I) are administered by intraarterial or intravenous route in dosages ranging from 1 x 10 (to the power of 4) -1 x 10 (to the power of 12) infectious particles.

EXAMPLE - **Expression** of myocardin 1 was determined by whole-mount or section in situ hybridizations to mouse embryos at E7.75 and E12.5. The results illustrated the **expression** pattern of myocardin 1 during early heart development. At E13.5, myocardin **expression** was evident within smooth muscle cells lining the walls of the esophagus and aortic arch arteries, as well as the pulmonary outflow tract. **Expression** in these smooth muscle cell types was still apparent, but was diminished, by E15.5. Myocardin **expression** was also detected in smooth muscle cells within the lung and gut, as well as in head mesenchyme, which may serve as a source of smooth muscle cell precursors. Myocardin was not **expressed** at **expressed** in detectable levels in skeletal muscle. The **expression** of myocardin 1 transcripts in adult mouse tissues was analyzed by Northern blot. The results showed that the transcripts were detected only in the heart. To determine the function of myocardin 1, myocardin 1 **expression** plasmids were transfected into fibroblasts (COS and HeLa cells) along with **expression** plasmids for the cardiac transcription factor GATA4. 0.1 micrograms of **expression** plasmid encoding myocardin 1 along with the luciferase

plasmids were mixed with 3 mul of the FuGENE 6 and added to cells in six-well plates. Cells were harvested 48 hr later and luciferase activity was determined in cell extracts. Cytomegalovirus (CMV)-lacZ which contains the lacZ gene under the control of the constitutive cytomegalovirus promoter was included in all transfections as an internal control. to normalize the variations in transfection efficiency. The results demonstrated that myocardin 1, plus GATA4, transctivates regulatory sequences for the cardiac specific homeobox Nkx2.5, which is the earliest marker for the cardiac lineage in vertebrates. Initial searches of DNA sequence databases with myocardin 1 sequence revealed a number of related sequences. Most of these sequences were short sequences (for e.g. **expressed** sequence tags (ESTs)) that shared **homology** to only small regions of myocardin 1. None of the sequences located were identified as encoding proteins having any particular function, much less any function related to cell regulation, particularly cardiac cell regulation. However, using these techniques in combination with the information obtained previously regarding the murine myocardin. Two sequences were identified that shared significant **homology** with myocardin 1. These appeared to be partial sequences from two additional myocardin genes. cDNA **clones** for these two related genes, now designated myocardin 2 and myocardin 3 were obtained. A comparison of the three myocardin species identified revealed localized regions of high amino acid **homology** between the proteins, particularly in the carboxyl-terminal transcription activation domain. By Northern analysis, it was shown that the myocardin 2 was ubiquitous, and that myocardin 3 appeared restricted to heart and liver.(104 pages)

L10 ANSWER 27 OF 93 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-03597 BIOTECHDS
TITLE: Enhancing cardiac function in a mammal for treating heart disease such as congestive heart failure, by delivering to the heart of the mammal a vector comprising a gene encoding a beta-adrenergic signaling protein;
virus vector **expression** in host use in disease gene therapy
AUTHOR: HAMMOND H K; INSEL P A; PING P; POST S R; GAO M
PATENT ASSIGNEE: HAMMOND H K; INSEL P A; PING P; POST S R; GAO M
PATENT INFO: US 2002103147 1 Aug 2002
APPLICATION INFO: US 2000-750240 26 Dec 2000
PRIORITY INFO: US 2000-750240 26 Dec 2000; US 1999-472667 27 Dec 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-690626 [74]
AB DERWENT ABSTRACT:
NOVELTY - Enhancing (M1) cardiac function in a mammal, involves delivering a vector to the heart of the mammal, where the vector comprises a gene encoding a beta-adrenergic signaling protein (beta-ASP) operably linked to a promoter.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a **recombinant** replication-defective viral particle (I) comprising a gene encoding a beta-ASP operably linked to a promoter; (2) a mammalian cell (II) transfected with (I); (3) a filtered adenovirus particle preparation (III) comprising (I), and a carrier; (4) generating (M2) (I), involves introducing first and second plasmids into a replication-permissive mammalian cell **expressing** one or more adenovirus genes conferring replication competence, where the first plasmid comprises a gene encoding a beta-ASP operably linked to a promoter and further comprises a replication-defective **human** adenovirus genome, and the second plasmid comprises a replication-proficient **human** adenovirus genome and further comprises an additional polynucleotide sequence making the second plasmid too large to be encapsidated in an adenovirus particle, where rescue recombination takes place between the first plasmid and the second plasmid to generate a **recombinant** adenoviral genome comprising

the gene encoding a beta-ASP but lacking one or more adenoviral replication genes, where the **recombinant** genome is sufficiently small to be encapsidated in an adenovirus particle, identifying successful **recombinant** viral vectors in cell culture, and propagating a resulting **recombinant** viral particle in replication-permissive mammalian cells **expressing** the missing adenoviral replication genes to generate a **recombinant** replication-defective viral particle; (5) a **recombinant** pro-viral plasmid (IV) comprising a gene encoding a beta-ASP operably linked to a promoter and further comprising a replication-defective viral genome; (6) a cell (V) comprising (IV); (7) a polynucleotide (VI) comprising a sequence encoding a chimeric adenylylcyclase polypeptide; (8) an isolated polynucleotide (VII) comprising a sequence encoding a **human** adenylylcyclase (ACVI) polypeptide comprising a sequence of 1168 amino acids fully defined in the specification, or its variant having adenylylcyclase activity; (9) an isolated polynucleotide (VIII) comprising a sequence of at least 100 nucleotides having 95% overall sequence identity with a sequence of comparable length within a sequence (S) of 314, 1812 or 3549 base pairs fully defined in the specification; (10) an isolated polypeptide (IX) encoded by (VI) or (VII); and (11) a vector comprising (VI) or (VII).

BIOTECHNOLOGY - Preferred Method: In M1, the vector is introduced into a blood vessel supplying blood to the myocardium of the heart, and is delivered to cardiac myocytes. The blood vessel supplying blood to the myocardium of the heart is a coronary artery, saphenous vein graft or internal mammary artery graft. The vector is introduced into both left and right coronary arteries. The vector comprises a gene encoding a beta-ASP such as beta-adrenergic receptor (beta-AR), G-protein receptor **kinase** inhibitor (GRK inhibitor) and an adenylylcyclase (AC). The vector comprises genes encoding two different beta-adrenergic signaling proteins operably linked to a promoter. The method further comprises introducing a second vector comprising a gene encoding a second beta-ASP operably linked to a promoter, where the second beta-ASP is different from the first beta-ASP. The beta-ASP is beta1-AR or beta2-AR. The gene encoding beta-ASP is a gene encoding GRK inhibitor. The beta-ASP is AC isoform VI comprising a sequence of 1167 or 1168 amino acids defined in the specification, and is encoded by a sequence comprising 3582 base pairs (bp) fully defined in the specification. The gene encoding beta-ASP is operably linked to a heterologous promoter such as heterologous constitutive promoter or heterologous inducible promoter. The promoter is ventricular **myosin light chain** 2 promoter and ventricular myosin heavy chain promoter. The gene encoding beta-ASP is a gene comprising a sequence of 3552 base pairs fully defined in the specification encoding **human** AC isoform VI operably linked to a heterologous promoter. The gene encoding beta-ASP is a variant of a wild-type beta-ASP gene comprising a deletion in one or more untranslated regions of the beta-ASP gene. The deletion removes 100 bp of the 3'-untranslated region. The gene encoding beta-ASP is a variant AC gene having a deletion of the 3'-translated region or truncated ACVI having a deletion removing the 3'-translated region. The vector is viral vector, a lipid-based vector, or a viral particle such as adenovirus (AV) or adeno-associated virus (AAV). The viral particle is an adenovirus comprising a polynucleotide having a promoter operably linked to a gene encoding a beta-ASP and the adenovirus vector is replication-defective in **humans**.

ACTIVITY - Cardiant.

MECHANISM OF ACTION - Enhancer of cardiac function (claimed); Gene therapy. In vivo gene transfer of an adenylylcyclase beta-ASP transgene to myocardium was studied. The ability to enhance beta-adrenergic responsiveness in vivo using gene therapy to deliver a beta-ASP transgene to the myocardium of a large animal model was studied. Animals included 3 domestic pigs. A left thoracotomy was performed under sterile conditions for instrumentation. Catheters were placed in the left atrium and aorta, providing a unit to calibrate the left ventricular high fidelity pressure

gauge used to measure pressure development, and to monitor pressures. Wires were sutured on the left atrium to permit ECG recording and atrial pacing. After recovery from surgery, pigs were examined to determine beta-adrenergic responsiveness and baseline left ventricular dimension and hemodynamics. The most important element of these studies were heart rate responses to isoproterenol infusion. One of the pigs was also examined for left ventricular dP/dt measurements that were made before and after gene transfer. Adenovirus vector system was used to deliver transgenes by in vivo gene delivery. As an exemplary beta-ASP transgene, the ACVI isoform was used. The vector material injected in vivo was highly purified and contained no wild-type (replication competent) adenovirus. Thus adenovirus infection and inflammatory infiltration in the heart were minimized. The vector preparation was injected into the lumen of the coronary artery by coronary catheters. Introduction of the vector preparation was made by injecting 2 ml into both the left and right coronary arteries. A very high efficiency gene delivery to the myocardium was obtained with no transgene **expression** observed in hepatocytes. Such in vivo gene delivery of a beta-ASP transgene to myocardium was found to enhance cardiac function in large mammal model.

USE - (M1) is useful for enhancing cardiac function in a mammal, preferably **human** (claimed). (M1) is specifically useful for treating heart diseases such as congestive heart failure.

ADMINISTRATION - The vector comprising the gene encoding beta-ASP is administered at a dose of 107, preferably 1011 viral particles by intracoronary injection.

EXAMPLE - Generation of a beta-adrenergic signaling protein (beta-ASP) transgene using a **human** adenylylcyclase gene was as follows: A **human** heart cDNA library was screened with an SphI fragment of about 1.9 kb from the murine adenylylcyclase (ACVI) (ACVI) cDNA using standard molecular biological techniques. Six positive **clones** were identified in the primary screen and confirmed in secondary and tertiary screens. Three of these **clones** (designated **clones** 1, 4 and 5) were sub-**cloned** into a vector for sequencing and a Bluescript vector pBS-SK was employed. The first round of sequencing was carried out using T3 and T7 primers, and then internal primers were employed for subsequent sequencing. All three of the **clones** contained sequences that were highly **homologous** to ACVI genes of other species including the mouse. These **clones**, or its sub-fragments, were used to identify overlapping **clones** containing the remaining sequence. From the overlapping **clones** a nucleotide sequence comprising 314 or 1812 base pairs fully defined in the specification was obtained, which corresponded to more than 2 kb of presumed 3.4 kb coding sequence of **human** ACVI. The sequence encoded a polypeptide having 104 or 604 amino acids fully defined in the specification. From the sequence information provided in the above nucleotide sequence, the complete nucleotide sequence encoding the full length **human** ACVI or its variants was readily obtained using standard **recombinant** DNA methodology. The complete nucleotide sequence of **human** ACVI had 3549 base pairs fully defined in the specification and encoded a sequence of 1167 amino acids fully defined in the specification. (69 pages)

L10 ANSWER 28 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:594888 HCAPLUS
DOCUMENT NUMBER: 137:136153
TITLE: cDNAs encoding myocardin and their use in cardiac transcriptional activation in heart development
INVENTOR(S): Olson, Eric N.; Wang, Da-Shi
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 175 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060946	A2	20020808	WO 2001-US50606	20011221
WO 2002060946	A3	20030605		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1345962	A2	20030924	EP 2001-998118	20011221

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: WO 2001-US50606 W 20011221

AB The present invention relates to a novel cardiac-specific mouse transcription factor myocardin and **human** myocardin sequence **homologs**. This mol. modulates the development and differentiation of cardiomyocytes and is a potent inhibitor of cell growth. Methods to exploit these observations are provided and include re-specifying non-cardiac cells into cardiac cells, stimulating cardiac tissue regeneration, and methods for treating cardiomyopathies, myocardial infarction. Myocardin belongs to the SAP domain family of nuclear proteins and activates cardiac muscle promoters by associating with SRF. **Expression** of a dominant neg. mutant of myocardin in Xenopus embryos interferes with myocardial cell differentiation. Myocardin is the founding member of a class of muscle transcription factors and provides a mechanism whereby SRF can convey myogenic activity to cardiac muscle genes. To determine the functions of myocardin 1, plasmids synthesizing myocardin 1 were transfected into fibroblasts along with **expression** plasmids for cardiac transcription factor GATA4. The results showed that myocardin 1 plus GATA4 trans-activate cardiac specific homeobox Nkx2.5 regulatory sequences, which is the earliest marker for cardiac lineage in vertebrates. Thus, myocardin 1 plays an important role in regulating cardiomyocyte development.

L10 ANSWER 29 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2002:285556 HCAPLUS
DOCUMENT NUMBER:	137:45438
TITLE:	**Expressed** gene sets as markers for specific tumors
INVENTOR(S):	Ramaswamy, Sridhar; Golub, Todd B.; Tamayo, Pablo; Angelo, Michael
PATENT ASSIGNEE(S):	Whitehead Institute for Biomedical Research, USA; Dana-Farber Cancer Institute, Inc.
SOURCE:	PCT Int. Appl., 715 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024956	A2	20020328	WO 2001-XA29287	20010919

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, RO,

RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
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BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2002024956 A2 20020328 WO 2001-US29287 20010919
WO 2002024956 C1 20030306
WO 2002024956 A3 20030626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-233534P P 20000919
US 2001-278749P P 20010326
WO 2001-US29287 W 20010919

AB Sets of genetic markers for specific tumor classes are described, as well as methods of identifying a biol. sample based on these markers. Total RNA was isolated from .apprx.300 **human** tumor and normal tissue specimens representing 30 individual classes of tumor or normal tissue, and cDNA produced using established mol. biol. protocols was hybridized to two high d. Affymetrix oligonucleotide microarrays (Hu6800FL and Hu35KsubA0). Raw **expression** data was combined into a master data set containing the **expression** values for between 6800 and 16,000 genes **expressed** by each individual sample. A filter was applied to this data set which only allows those genes **expressed** at 3-fold above baseline and with an absolute difference in **expression** value of 100 to pass. By comparing the sets of genes which are **expressed** specifically in one class of tumor (e.g., pancreatic adenocarcinoma) vs. its accompanying normal tissue (e.g., normal pancreas), sets of genes were determined which are specific to various tumors and their normal tissue counterparts. Also described are diagnostic, prognostic, and therapeutic screening uses for these markers, as well as oligonucleotide arrays comprising these markers. [This abstract record is one of 4 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 30 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:51660 HCAPLUS
DOCUMENT NUMBER: 136:98853
TITLE: Proteins and nucleic acids associated with aging and their detection in identification of tissues undergoing senescence and of senescence modulators
INVENTOR(S): Burmer, Glenna; Pritchard, David; Brown, Joseph P.; Demas, Vasiliki
PATENT ASSIGNEE(S): Lifespan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004662	A1	20020117	WO 2001-US21361	20010703

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,

KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002098495 A1 20020725 US 2001-898730 20010703
PRIORITY APPLN. INFO.: US 2000-216470P P 20000706

AB This invention relates to the discovery of nucleic acids and proteins associated with the aging processes, such as cell proliferation and senescence. The identification of these aging-associated nucleic acids and proteins have diagnostic uses in detecting the aging status of a cell population as well as applications for gene therapy and the delaying of the aging process.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 31 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313

PRIORITY APPLN. INFO.: JP 2001-73183 A 20010314
JP 2001-74993 A 20010315
JP 2001-102519 A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose **expression** is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L10 ANSWER 32 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002439646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12177420
TITLE: Caspase 3 activity is required for skeletal muscle differentiation.
AUTHOR: Fernando Pasan; Kelly John F; Balazsi Kim; Slack Ruth S; Megeney Lynn A
CORPORATE SOURCE: Ottawa Health Research Institute, Molecular Medicine Program, Ottawa General Hospital, Ottawa, ON, Canada K1H 8L6.

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 Aug 20) 99 (17) 11025-30. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020829
Last Updated on STN: 20030105
Entered Medline: 20020927

AB The cellular alterations associated with skeletal muscle differentiation share a high degree of similarity with key phenotypic changes usually ascribed to apoptosis. For example, actin fiber disassembly/reorganization is a conserved feature of both apoptosis and differentiating myoblasts and the conserved muscle contractile protein, **myosin light chain kinase**, is required for the apoptotic feature of membrane blebbing. As such, these observations suggest that the induction of differentiation and apoptosis in the myogenic lineage may use overlapping cellular mechanisms. Here, we report that skeletal muscle differentiation depends on the activity of the key apoptotic protease, caspase 3. Peptide inhibition of caspase 3 activity or **homologous** deletion of caspase 3 leads to dramatic reduction in both myotube/myofiber formation and **expression** of muscle-specific proteins. Subsequently, we have identified Mammalian Sterile Twenty-like **kinase** as a crucial caspase 3 effector in this cellular process. Mammalian Sterile Twenty-like **kinase** is cleavage-activated by caspase 3, and restoration of this truncated **kinase** in caspase 3 null myoblasts restores the differentiation phenotype. Taken together, these results confirm a unique and unanticipated role for a caspase 3-mediated signal cascade in the promotion of myogenesis.

L10 ANSWER 33 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002130070 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11748245
TITLE: Activation of smooth muscle **myosin light chain kinase** by calmodulin. Role of LYS(30) and GLY(40).
AUTHOR: Van Lierop Jacquelyn E; Wilson David P; Davis Jonathan P; Tikunova Svetlana; Sutherland Cindy; Walsh Michael P; Johnson J David
CORPORATE SOURCE: Smooth Muscle Research Group and the Canadian Institutes of Health Research Group in Regulation of Vascular Contractility, Department of Biochemistry and Molecular Biology, University of Calgary Faculty of Medicine, Calgary, Alberta T2N 4N1, Canada.
CONTRACT NUMBER: DK33727 (NIDDK)
SOURCE: Journal of biological chemistry, (2002 Feb 22) 277 (8) 6550-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20030105
Entered Medline: 20020424

AB Calmodulin (CaM)-dependent **myosin light chain kinase** (**MLCK**) plays a key role in activation of smooth muscle contraction. A soybean isoform of CaM, SCaM-4 (77% identical to **human** CaM) fails to activate **MLCK**, whereas SCaM-1 (90.5% identical to **human** CaM) is as effective as CaM. We exploited

this difference to gain insights into the structural requirements in CaM for activation of **MLCK**. A chimera (domain I of SCaM-4 and domains II-IV of SCaM-1) behaved like SCaM4, and analysis of site-specific mutants of SCaM-1 indicated that K30E and G40D mutations were responsible for the reduction in activation of **MLCK**. Competition experiments showed that SCaM-4 binds to the CaM-binding site of **MLCK** with high affinity. Replacement of CaM in skinned smooth muscle by exogenous CaM or SCaM-1, but not SCaM-4, restored Ca(2+)-dependent contraction. K30E/M36I/G40D SCaM-1 was a poor activator of contraction, but site-specific mutants, K30E, M36I and G40D, each restored Ca(2+)-induced contraction to CaM-depleted skinned smooth muscle, consistent with their capacity to activate **MLCK**. Interpretation of these results in light of the high-resolution structures of (Ca(2+))(4)-CaM, free and complexed with the CaM-binding domain of **MLCK**, indicates that a surface domain containing Lys(30) and Gly(40) and residues from the C-terminal domain is created upon binding to **MLCK**, formation of which is required for activation of **MLCK**. Interactions between this activation domain and a region of **MLCK** distinct from the known CaM-binding domain are required for removal of the autoinhibitory domain from the active site, i.e., activation of **MLCK**, or this domain may be required to stabilize the conformation of (Ca(2+))(4)-CaM necessary for **MLCK** activation.

L10 ANSWER 34 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:390563 HCAPLUS
DOCUMENT NUMBER: 137:107242
TITLE: Development of a highly specialized cDNA array for the study and diagnosis of epithelial ovarian cancer
AUTHOR(S): Sawiris, G. Peter; Sherman-Baust, Cheryl A.; Becker, Kevin G.; Cheadle, Chris; Teichberg, Diane; Morin, Patrice J.
CORPORATE SOURCE: Laboratory of Cellular and Molecular Biology, Gerontology Research Center, National Institute on Aging, Baltimore, MD, 21224, USA
SOURCE: Cancer Research (2002), 62(10), 2923-2928
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovarian cancer is a major cause of cancer death in women. Unfortunately, the mol. pathways underlying ovarian cancer progression are poorly understood, making the development of novel diagnostic and therapeutic strategies difficult. On the basis of our previous observations obtained from serial anal. of gene **expression**, we have constructed a specialized cDNA array for the study of ovarian cancer. Small, specialized arrays have several practical advantages and can reveal information that is lost in the "noise" generated by irrelevant genes present in larger arrays. The array, which we named Ovachip, contains 516 cDNAs chosen from our serial anal. of gene **expression** and cDNA array studies for their relevance to ovarian cancer. The gene **expression** patterns revealed with the Ovachip are highly reproducible and extremely consistent among the different ovarian specimens tested. This array was extremely sensitive at differentiating ovarian cancer from colon cancer based on **expression** profiles. The Ovachip revealed clusters of coordinately **expressed** genes in ovarian cancer. One such cluster, the IGF2 cluster, is particularly striking and includes the insulin-like growth factor II, the cisplatin resistance-associated protein, the checkpoint suppressor 1, the cyclin-dependent **kinase** 6, and a protein tyrosine phosphatase receptor. We also identified a cluster of down-regulated genes that included the cyclin-dependent **kinase** 7 and cyclin H. Thus, the Ovachip allowed us to identify previously unidentified clusters of differentially **expressed** genes that may provide new paradigms

for mol. pathways important in ovarian malignancies. Because of the relevance of the arrayed genes, the Ovachip may become a powerful tool for investigators in the field of ovarian cancer and may facilitate progress in understanding the etiol. of this disease and in its clin. management.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 35 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002495533 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12356872
TITLE: P21-activated **kinase** 4 interacts with integrin alpha v beta 5 and regulates alpha v beta 5-mediated cell migration.
AUTHOR: Zhang Hongquan; Li Zhilun; Viklund Eva-Karin; Stromblad Staffan
CORPORATE SOURCE: Karolinska Institutet, Department of Microbiology, Pathology, and Immunology, SE-141 86 Huddinge, Sweden.
SOURCE: Journal of cell biology, (2002 Sep 30) 158 (7) 1287-97. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021002
Last Updated on STN: 20021213
Entered Medline: 20021104
AB p21-activated **kinase** 1 (PAK1) can affect cell migration (Price et al., 1998; del Pozo et al., 2000) and modulate **myosin light chain kinase** and LIM **kinase**, which are components of the cellular motility machinery (Edwards, D.C., L.C. Sanders, G.M. Bokoch, and G.N. Gill. 1999. Nature Cell Biol. 1:253-259; Sanders, L.C., F. Matsumura, G.M. Bokoch, and P. de Lanerolle. 1999. SCIENCE: 283:2083-2085). We here present a novel cell motility pathway by demonstrating that PAK4 directly interacts with an integrin intracellular domain and regulates carcinoma cell motility in an integrin-specific manner. Yeast two-hybrid screening identified PAK4 binding to the cytoplasmic domain of the integrin beta 5 subunit, an association that was also found in mammalian cells between endogenous PAK4 and integrin alpha v beta 5. Furthermore, we mapped the PAK4 binding to the membrane-proximal region of integrin beta 5, and identified an integrin-binding domain at aa 505-530 in the COOH terminus of PAK4. Importantly, engagement of integrin alpha v beta 5 by cell attachment to vitronectin led to a redistribution of PAK4 from the cytosol to dynamic lamellipodial structures where PAK4 colocalized with integrin alpha v beta 5. Functionally, PAK4 induced integrin alpha v beta 5-mediated, but not beta1-mediated, **human** breast carcinoma cell migration, while no changes in integrin cell surface **expression** levels were observed. In conclusion, our results demonstrate that PAK4 interacts with integrin alpha v beta 5 and selectively promotes integrin alpha v beta 5-mediated cell migration.

L10 ANSWER 36 OF 93 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002087381 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11814696
TITLE: Identification, tissue **expression** and chromosomal localization of **human** Obscurin-**MLCK**, a member of the titin and Dbl families of **myosin light chain kinases**.
AUTHOR: Russell Mark W; Raeker Maide O; Korytkowski Kristin A; Sonneman Kevin J
CORPORATE SOURCE: Department of Pediatrics and Communicable Diseases, Division of Pediatric Cardiology, University of Michigan, Ann Arbor, MI 48109, USA.. mruss@umich.edu

SOURCE: Gene, (2002 Jan 9) 282 (1-2) 237-46.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020130
Last Updated on STN: 20020403
Entered Medline: 20020328

AB Members of the Dbl family of guanine nucleotide exchange factors (GEFs) have important roles in the organization of actin-based cytoskeletal structures of a wide variety of cell types. Through the activation of members of the Rho family of GTP signaling molecules, these exchange factors elicit cytoskeletal alterations that allow cellular remodeling. As important regulators of RhoGTPase activity, members of this family are candidates for mediating the RhoGTPase activation and cytoskeletal changes that occur during cardiac development and during the myocardial response to hypertrophic stimuli. In this study, we characterize a novel **human** gene that is **expressed** in skeletal and cardiac muscle and has putative functional domains similar to those found in members of both the Dbl family of GEFs and the titin family of **myosin light chain kinases** (**MLCK**). The cDNA sequence of this gene, which has been designated Obscurin-**myosin light chain kinase** (Obscurin-**MLCK**), would be predicted to encode for at least 68 immunoglobulin domains, two fibronectin domains, one calcium/calmodulin binding domain, a RhoGTP exchange factor domain, and two serine-threonine **kinase** domains. The combination of the putative Rho GEF and two **kinase** domains has not been noted in any other members of the titin or Dbl families. Alternative splicing allows the generation of a number of unique Obscurin-**MLCK** isoforms that contain various combinations of the functional domains. One group of isoforms is comparable to Unc-89, a Caenorhabditis elegans sarcomere-associated protein, in that they contain a putative RhoGEF domain and multiple immunoglobulin repeats. Other isoforms more closely resemble **MLCK** , containing one or both of the putative carboxy-terminal serine-threonine **kinase** domains. The modular nature of the Obscurin-**MLCK** isoforms indicates that it may have an array of functions important to cardiac and skeletal muscle physiology.

L10 ANSWER 37 OF 93 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003496530 EMBASE
TITLE: Role of Ca(2+) signaling in the regulation of endothelial permeability.
AUTHOR: Tiruppathi C.; Minshall R.D.; Paria B.C.; Vogel S.M.; Malik A.B.
CORPORATE SOURCE: C. Tiruppathi, Department of Pharmacology M/C868, College of Medicine, University of Illinois at Chicago, 835 S. Wolcott Avenue, Chicago, IL 60612, United States. tiruc@uic.edu
SOURCE: Vascular Pharmacology, (1 Nov 2002) 39/4-5 (173-185).
Refs: 75
ISSN: 1537-1891 CODEN: VPAHAJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The vascular endothelial cell forms a semipermeable barrier between blood and interstitium. Inflammatory mediators such as thrombin and histamine induce vascular leakage defined as increased endothelial permeability to plasma proteins and other solutes. Increased endothelial permeability is

the hallmark of inflammatory vascular edema. Inflammatory mediators that bind to heptahelical G protein-coupled receptors (GPCR) trigger increased endothelial permeability by increasing the intracellular Ca(2+) concentration ([Ca(2+)](i)). The rise in [Ca(2+)](i) activates key signaling pathways, which mediate cytoskeletal reorganization (through **myosin light chain** (MLC)-dependent contraction) and disassembly of VE-cadherin at the adherens junctions. The Ca(2+)-dependent protein **kinase** C (PKC) isoform, PKC-α, plays a critical role in initiating endothelial cell contraction and disassembly of VE-cadherin junctions. The increase in [Ca(2+)](i) induced by a variety of agonists is achieved by the generation of inositol 1,4,5-trisphosphate (IP3), activation of IP3 receptors (IP3R), release of stored intracellular Ca(2+), and Ca(2+) entry through plasma membrane channels. Recent findings demonstrate that IP3-sensitive Ca(2+) store depletion activates plasma membrane cation channels (i.e., store-operated cation channels (SOC) or Ca (2+) release activated channels) to cause Ca(2+) influx in endothelial cells. This mode of Ca(2+) influx is also known as capacitative Ca(2+) entry (CCE). Store-operated Ca(2+) influx signals increase in permeability and nitric oxide (NO) production and provokes changes in gene **expression** in endothelial cells. Recent studies have established that the Drosophila transient receptor potential (TRP) gene family of channels **expressed** in endothelial cells can function as SOC. Deletion of one of the TRP **homologues**, TRPC4, in mouse caused impairment in store-operated Ca(2+) current and Ca(2+) store release activated Ca (2+) influx in aortic and lung endothelial cells (LEC). In TRPC4 knockout (TRPC4(-/-)) mice, acetylcholine-induced endothelium- dependent smooth muscle relaxation was drastically reduced. In addition, TRPC4(-/-) mice LEC exhibited lack of actin stress fiber formation and cell retraction in response to thrombin activation of proteinase-activated receptor-1 (PAR-1) in endothelial cells. The increase in lung microvascular permeability in response to thrombin receptor activation was inhibited in TRPC4(-/-) mice. These results indicate that endothelial TRP channels such as TRPC1 and TRPC4 play an important role in signaling the increase in endothelial permeability.

L10 ANSWER 38 OF 93 EMBASE on STN

ACCESSION NUMBER: 2003079961 EMBASE
TITLE: Cell adhesion and matrix remodeling genes identified by co-**expression** analysis.
AUTHOR: Walker M.G.; Volkmuth W.
CORPORATE SOURCE: M.G. Walker, Walker Bioscience, 1475 Flamingo Way, Sunnyvale, CA, United States. mwalker@stanfordalumni.org
SOURCE: Gene Function and Disease, (2002) 3/3-4 (109-112).
Refs: 4
ISSN: 1438-7506 CODEN: GFDEAS
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cell adhesion and matrix remodeling are elements in many diseases, ranging from atherosclerosis and fibrosis to metastatic cancer. However, many genes that participate in these processes have not yet been identified. To find such genes, we looked for previously uncharacterized genes that are co-**expressed** with known cell adhesion and matrix remodeling genes. The known genes in this study included MMP2, TIMP3, BM-40, chondroitin, connective tissue growth factor, fibromodulin, IGFBP5, laminin, MGP, **myosin light chain kinase**, several collagens, and other matrix and adhesion proteins. We found eight previously uncharacterized genes, here named MXRA1 through

MXRA8, that were strongly co-**expressed** with these known adhesion and matrix genes. Five of the MXRA genes have a significant similarity to uncharacterized cDNA sequences or predicted proteins listed in the Genbank database, but otherwise show distant or no sequence similarity to genes with known function. Subsequent to our entry of the MXRA gene sequences in the Genbank, three of the eight genes have been independently described by other researchers: MXRA2 is a-parvin, a cell-matrix adhesion protein, MXRA4 is a C1 complement component receptor involved in cell adhesion, and MXRA5 is adlican, an adhesion proteoglycan. The analysis described here provides further evidence for the role of these genes in adhesion and matrix remodeling.

L10 ANSWER 39 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:798473 HCAPLUS
DOCUMENT NUMBER: 135:340282
TITLE: Nucleic acid sequences associated with baldness and uses in detecting the likelihood of baldness and for gene therapy
INVENTOR(S): Pritchard, David; Burmer, Glenna; Brown, Joseph; Demas, Vasiliki
PATENT ASSIGNEE(S): Lifespan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081628	A1	20011101	WO 2001-US12184	20010413
WO 2001081628	C2	20021227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002177566	A1	20021128	US 2001-825096	20010402

PRIORITY APPLN. INFO.: US 2000-199745P P 20000425
AB This invention relates to the discovery of nucleic acids and proteins associated with baldness and/or hair loss. A change in gene **expression** associated with baldness, in samples from male, **human** scalp, was demonstrated. The gene **expression** from non-bald individual or in a non-bald region of the scalp of an individual was compared with the gene **expression** in a bald individual or in a non-bald region of the scalp of an individual, and also with transitional individual or with transitional regions of the scalp. The identification of the baldness-associated nucleic acids and proteins have uses in predicting the propensity for baldness of an individual and/or in determining the likelihood of baldness in an individual experiencing hair loss. In addition, the nucleic acids of the invention can be used can be used for gene therapy for delaying or stopping the progression of baldness, and/or for reversing baldness.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 40 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:763251 HCAPLUS
DOCUMENT NUMBER: 135:299597
TITLE: Genes differentially **expressed** in

human foam cell differentiation
INVENTOR(S): Shiffman, Dov; Somogyi, Roland; Lawn, Richard; Seilhamer, Jeffrey J.; Porter, Gordon J.; Mikita, Thomas; Tai, Julie
PATENT ASSIGNEE(S): Incyte Genomics, Inc., USA
SOURCE: PCT Int. Appl., 315 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077389	A2	20011018	WO 2001-US11128	20010404
WO 2001077389	A3	20030424		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1358347	A2	20031105	EP 2001-924723	20010404
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
US 2003165924	A1	20030904	US 2002-240965	20021004

PRIORITY APPLN. INFO.: US 2000-195106P P 20000405
WO 2001-US11128 W 20010404

AB The present invention relates to 276 purified polynucleotides and compns. comprising pluralities of polynucleotides that are differentially **expressed** during **human** foam cell development and are associated with atherosclerosis. The present invention presents the use of the compns. as elements immobilized on a substrate for hybridization, and provides methods for using the compns. and polynucleotides in the diagnosis of conditions, disorders, and diseases associated with atherosclerosis.

L10 ANSWER 41 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:320060 HCAPLUS
DOCUMENT NUMBER: 134:339179
TITLE: Nucleic acids and proteins associated with cancer as antitumor targets
INVENTOR(S): Burmer, Glenna C.; Brown, Joseph P.; Pritchard, David
PATENT ASSIGNEE(S): Lifespan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030964	A2	20010503	WO 2000-US29126	20001020
WO 2001030964	A3	20010809		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001013397 A5 20010508 AU 2001-13397 20001020

PRIORITY APPLN. INFO.: US 1999-161232P P 19991022
US 2000-693783 A 20001019
WO 2000-US29126 W 20001020

AB This invention relates to the discovery of nucleic acids associated with cell proliferation, neoplasia, cell transformation, malignant tumor formation and metastasis and uses therefor. The present invention provides a method for cancer diagnosing by detecting the overexpression or the underexpression of a cancer-associated mRNA in the tissue of interest, preferably in liver, breast, prostate, kidney and colon. In another aspect, the invention provides methods for arresting cancer and a method for identifying a modulators of cancer development.

L10 ANSWER 42 OF 93 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 2001565171 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11485996

TITLE: Identification of a new form of death-associated protein **kinase** that promotes cell survival.

AUTHOR: Jin Y; Blue E K; Dixon S; Hou L; Wysolmerski R B; Gallagher P J

CORPORATE SOURCE: Department of Cellular and Integrated Physiology, Indiana University School of Medicine, 635 Barnhill Dr., Indianapolis, IN 46202, USA.

CONTRACT NUMBER: RO1 HL45788 (NHLBI)
RO1 HL54118 (NHLBI)

SOURCE: Journal of biological chemistry, (2001 Oct 26) 276 (43) 39667-78.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 20011023
Last Updated on STN: 20030105
Entered Medline: 20011207

AB In this study, two alternatively spliced forms of the mouse death-associated protein **kinase** (DAPK) have been identified and their roles in apoptosis examined. The mouse DAPK-alpha sequence is 95% identical to the previously described **human** DAPK, and it has a **kinase** domain and calmodulin-binding region closely related to the 130-150 kDa **myosin light chain kinases**. A 12-residue extension of the carboxyl terminus of DAPK-beta distinguishes it from the **human** and mouse DAPK-alpha. DAPK phosphorylates at least one substrate in vitro and in vivo, the myosin II regulatory light chain. This phosphorylation occurs preferentially at Ser-19 and is stimulated by calcium and calmodulin. The mRNA encoding DAPK is widely distributed and detected in mouse embryos and most adult tissues, although the **expression** of the encoded 160-kDa DAPK protein is more restricted. Overexpression of DAPK-alpha, the mouse **homolog** of **human** DAPK has a negligible effect on tumor necrosis factor (TNF)-induced apoptosis. Overexpression of DAPK-beta has a strong cytoprotective effect on TNF-treated cells. Biochemical analysis of TNF-treated cell lines **expressing** mouse DAPK-beta suggests that the cytoprotective effect of DAPK is mediated through both intrinsic and extrinsic apoptotic signaling pathways and results in the inhibition of cytochrome c release from the mitochondria as well as inhibition of caspase-3 and caspase-9 activity. These results suggest that the mouse DAPK-beta is a negative regulator of TNF-induced apoptosis.

L10 ANSWER 43 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001429709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11384979
TITLE: Zipper-interacting protein **kinase** induces Ca(2+)-free smooth muscle contraction via **myosin light chain** phosphorylation.
AUTHOR: Niiro N; Ikebe M
CORPORATE SOURCE: Department of Physiology, University of Massachusetts Medical School, Worcester, Massachusetts 01655, USA.
CONTRACT NUMBER: AR41653 (NIAMS)
HL60831 (NHLBI)
HL61426 (NHLBI)
SOURCE: Journal of biological chemistry, (2001 Aug 3) 276 (31) 29567-74.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20030105
Entered Medline: 20010913

AB The inhibition of myosin phosphatase evokes smooth muscle contraction in the absence of Ca(2+), yet the underlying mechanisms are not understood. To this end, we have **cloned** smooth muscle zipper-interacting protein (ZIP) **kinase** cDNA. ZIP **kinase** is present in various smooth muscle tissues including arteries. Triton X-100 skinning did not diminish ZIP **kinase** content, suggesting that ZIP **kinase** associates with the filamentous component in smooth muscle. Smooth muscle ZIP **kinase** phosphorylated smooth muscle myosin as well as the isolated 20-kDa **myosin light chain** in a Ca(2+)/calmodulin-independent manner. ZIP **kinase** phosphorylated **myosin light chain** at both Ser(19) and Thr(18) residues with the same rate constant. The actin-activated ATPase activity of myosin increased significantly following ZIP **kinase**-induced phosphorylation. Introduction of ZIP **kinase** into Triton X-100-permeabilized rabbit mesenteric artery provoked a Ca(2+)-free contraction. A protein phosphatase inhibitor, microcystin LR, also induced contraction in the absence of Ca(2+), which was accompanied by an increase in both mono- and diphosphorylation of **myosin light chain**. The observed sensitivity of the microcystin-induced contraction to various protein **kinase** inhibitors was identical to the sensitivity of isolated ZIP **kinase** to these inhibitors. These results suggest that ZIP **kinase** is responsible for Ca(2+) independent myosin phosphorylation and contraction in smooth muscle.

L10 ANSWER 44 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001341562 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278951
TITLE: Ca2+-independent smooth muscle contraction. a novel function for integrin-linked **kinase**.
AUTHOR: Deng J T; Van Lierop J E; Sutherland C; Walsh M P
CORPORATE SOURCE: Smooth Muscle Research Group and Canadian Institutes of Health Research Group in Regulation of Vascular Contractility, Department of Biochemistry, University of Calgary Faculty of Medicine, Calgary, Alberta T2N 4N1, Canada.
SOURCE: Journal of biological chemistry, (2001 May 11) 276 (19) 16365-73.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF296130
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20030105
Entered Medline: 20010614

AB Smooth muscle contraction follows an increase in cytosolic Ca(2+) concentration, activation of **myosin light chain kinase**, and phosphorylation of the 20-kDa light chain of myosin at Ser(19). Several agonists acting via G protein-coupled receptors elicit a contraction without a change in [Ca(2+)](i) via inhibition of **myosin light chain** phosphatase and increased myosin phosphorylation. We showed that microcystin (phosphatase inhibitor)-induced contraction of skinned smooth muscle occurred in the absence of Ca(2+) and correlated with phosphorylation of **myosin light chain** at Ser(19) and Thr(18) by a **kinase** distinct from **myosin light chain kinase**. In this study, we identify this **kinase** as integrin-linked **kinase**. Chicken gizzard integrin-linked **kinase** cDNA was **cloned**, sequenced, **expressed** in E. coli, and shown to phosphorylate **myosin light chain** in the absence of Ca(2+) at Ser(19) and Thr(18). Subcellular fractionation revealed two distinct populations of integrin-linked **kinase**, including a Triton X-100-insoluble component that phosphorylates myosin in a Ca(2+)-independent manner. These results suggest a novel function for integrin-linked **kinase** in the regulation of smooth muscle contraction via Ca(2+)-independent phosphorylation of myosin, raise the possibility that integrin-linked **kinase** may also play a role in regulation of nonmuscle motility, and confirm that integrin-linked **kinase** is indeed a functional protein-serine/threonine **kinase**.

L10 ANSWER 45 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001312581 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11113114
TITLE: Differential regulation of alternatively spliced endothelial cell **myosin light chain kinase** isoforms by p60(Src).
AUTHOR: Birukov K G; Csortos C; Marzilli L; Dudek S; Ma S F; Bresnick A R; Verin A D; Cotter R J; Garcia J G
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21224, USA.
CONTRACT NUMBER: HL50533 (NHLBI)
HL58064 (NHLBI)
SOURCE: Journal of biological chemistry, (2001 Mar 16) 276 (11) 8567-73.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

AB The Ca(2+)/calmodulin-dependent endothelial cell **myosin light chain kinase** (**MLCK**) triggers actomyosin contraction essential for vascular barrier regulation and leukocyte diapedesis. Two high molecular weight **MLCK** splice variants, EC **MLCK**-1 and EC **MLCK**-2 (210-214 kDa), in **human** endothelium are identical except for a deleted single exon in **MLCK**-2 encoding a 69-amino acid stretch (amino acids 436-505)

that contains potentially important consensus sites for phosphorylation by p60(Src) **kinase** (Lazar, V., and Garcia, J. G. (1999) Genomics 57, 256-267). We have now found that both **recombinant** EC **MLCK** splice variants exhibit comparable enzymatic activities but a 2-fold reduction of V(max), and a 2-fold increase in K(0.5 CaM) when compared with the SM **MLCK** isoform, whereas K(m) was similar in the three isoforms. However, only EC **MLCK**-1 is readily phosphorylated by purified p60(Src) in vitro, resulting in a 2- to 3-fold increase in EC **MLCK**-1 enzymatic activity (compared with EC **MLCK**-2 and SM **MLCK**). This increased activity of phospho-**MLCK**-1 was observed over a broad range of submaximal [Ca(2+)] levels with comparable EC(50) [Ca(2+)] for both phosphorylated and unphosphorylated EC **MLCK**-1. The sites of tyrosine phosphorylation catalyzed by p60(Src) are Tyr(464) and Tyr(471) within the 69-residue stretch deleted in the **MLCK**-2 splice variant. These results demonstrate for the first time that p60(Src)-mediated tyrosine phosphorylation represents an important mechanism for splice variant-specific regulation of nonmuscle **MLCK** and vascular cell function.

L10 ANSWER 46 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:712142 HCAPLUS
DOCUMENT NUMBER: 136:35557
TITLE: Distinctive molecular profiles of high-grade and low-grade gliomas based on oligonucleotide microarray analysis
AUTHOR(S): Rickman, David S.; Bobek, Miroslav P.; Misek, David E.; Kuick, Rork; Blaivas, Mila; Kurnit, David M.; Taylor, Jeremy; Hanash, Samir M.
CORPORATE SOURCE: Departments of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, 48109, USA
SOURCE: Cancer Research (2001), 61(18), 6885-6891
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Astrocytomas are heterogeneous intracranial glial neoplasms ranging from the highly aggressive malignant glioblastoma multiforme (GBM) to the indolent, low-grade pilocytic astrocytoma. We have investigated whether DNA microarrays can identify gene **expression** differences between high-grade and low-grade glial tumors. We compared the transcriptional profile of 45 astrocytic tumors including 21 GBMs and 19 pilocytic astrocytomas using oligonucleotide-based microarrays. Of the .apprx.6800 genes that were analyzed, a set of 360 genes provided a mol. signature that distinguished between GBMs and pilocytic astrocytomas. Many transcripts that were increased in GBM were not previously associated with gliomas and were found to encode proteins with properties that suggest their involvement in cell proliferation or cell migration. Microarray-based data for a subset of genes was validated using real-time quant. reverse transcription-PCR. Immunohistochem. anal. also localized the protein products of specific genes of interest to the neoplastic cells of high-grade astrocytomas. Our study has identified a large number of novel genes with distinct **expression** patterns in high-grade and low-grade gliomas.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 47 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:473659 HCAPLUS
DOCUMENT NUMBER: 135:205729
TITLE: Microarray analysis of the in vivo effects of hypophysectomy and growth hormone treatment on gene **expression** in the rat
AUTHOR(S): Flores-Morales, Amilcar; Stahlberg, Nina;

Tollet-Egnell, Petra; Lundeberg, Joakim; Malek, Renae L.; Quackenbush, John; Lee, Norman H.; Norstedt, Gunnar

CORPORATE SOURCE: Department of Molecular Medicine, Karolinska Institute, Stockholm, 17176, Swed.

SOURCE: Endocrinology (2001), 142(7), 3163-3176
CODEN: ENDOAO; ISSN: 0013-7227

PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors used cDNA microarrays containing 3000 different rat genes to study the consequences of severe hormonal deficiency (hypophysectomy) on the gene **expression** patterns in heart, liver, and kidney. Hybridization signals were seen from a majority of the arrayed cDNAs; nonetheless, tissue-specific **expression** patterns could be delineated. Hypophysectomy affected the **expression** of genes involved in a variety of cellular functions. Between 16-29% of the detected transcripts from each tissue changed **expression** level as a reaction to this condition. Chronic treatment of hypophysectomized animals with **human** GH also caused significant changes in gene **expression** patterns. The study confirms previous knowledge concerning certain gene **expression** changes in the above-mentioned situations and provides new information regarding hypophysectomy and chronic **human** GH effects in the rat. Furthermore, the authors have identified several new genes that respond to GH treatment. The results represent a first step toward a more global understanding of gene **expression** changes in states of hormonal deficiency.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 48 OF 93 EMBASE on STN

ACCESSION NUMBER: 2002163208 EMBASE

TITLE: Role of MgcRacGAP/Cyk4 as a regulator of the small GTPase Rho family in cytokinesis and cell differentiation.

AUTHOR: Kitamura T.; Kawashima T.; Minoshima Y.; Tonozuka Y.; Hirose K.; Nosaka T.

CORPORATE SOURCE: T. Kitamura, Division of Cellular Therapy, The Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan. kitamura@ims.u-tokyo.ac.jp

SOURCE: Cell Structure and Function, (2001) 26/6 (645-651).
Refs: 26
ISSN: 0386-7196 CODEN: CSFUDY

COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To identify the key molecules that regulate differentiation of hematopoietic cells, we carried out retrovirus-mediated functional screening for cDNAs whose **expression** suppresses IL-6-induced differentiation of mouse myeloid leukemic M1 cells. From this screening, we obtained a full length cDNA encoding a mouse **homologue** of **human** MgcRacGAP. Overexpression of the anti-sense MgcRacGAP profoundly inhibited IL-6-induced macrophage-differentiation of M1 cells. On the other hand, overexpression of the full-length form of MgcRacGAP alone enhanced macrophage differentiation of M1 cells in response to IL-6, and induced macrophage differentiation of HL-60 leukemic cells. To determine how this protein regulates differentiation and proliferation, an antibody against MgcRacGAP was prepared. Immunohistochemical studies revealed that MgcRacGAP mainly localizes in the nucleus in interphase, accumulates on the mitotic spindle in metaphase, and is condensed in the

midbody during cytokinesis. Overexpression of an N-terminal domain deletion mutant, which lacks the ability to localize to the midbody through association with tubulins, or a GAP-inactive mutant resulted in the formation of multinucleated cells in HeLa cells as well as in hemopoietic cells. Interestingly, MgcRacGAP in the midbody was phosphorylated probably on serine and threonine residues. These results indicate that MgcRacGAP regulates cytokinesis and cellular differentiation as a regulator of Rho family of GTPase and suggest that this process is controlled by some serine/threonine **kinases**.

L10 ANSWER 49 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001528231 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11574162
TITLE: Identification of myosin II **kinase** from sea urchin eggs as protein **kinase** CK2.
AUTHOR: Komaba S; Hamao H; Murata-Hori M; Hosoya H
CORPORATE SOURCE: Department of Biological Science, Graduate School of Science, Hiroshima University, Higashi-Hiroshima, 739-8526, Japan.
SOURCE: Gene, (2001 Sep 5) 275 (1) 141-8.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB024599
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20020420
Entered Medline: 20011213
AB Here we purified and identified a myosin II **kinase** from sea urchin eggs. The activity of this myosin II **kinase** in the egg extract was not significantly affected by Ca(2+)/calmodulin (CaM). Using sequential column chromatographies, we purified the myosin II **kinase** from the egg extract as a complex composed of 36- (p36) and 28-kDa (p28) proteins. Partial amino acid sequences of these two components were highly coincident with those of the alpha and beta subunits of protein **kinase** CK2 (formerly casein **kinase** II) in sea urchin eggs, respectively. To confirm that the purified myosin II **kinase** was CK2, we obtained a cDNA which encodes p36 from a cDNA library of sea urchin eggs. The amino acid sequence derived from the obtained cDNA showed over 70% **homology** to CK2 from various eukaryotes. Furthermore, **recombinant** p36, as well as the purified myosin II **kinase**, phosphorylated MRLC. One dimensional phosphopeptide mapping revealed that the phosphorylation site(s) of MRLC by both **recombinant** p36 and the purified myosin II **kinase** was identical. These clearly showed that the Ca(2+)/CaM-independent myosin II **kinase** activity in sea urchin eggs was identical to CK2.

L10 ANSWER 50 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001423954 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11472067
TITLE: The **myosin light chain** **kinase** gene is not duplicated in mouse: partial structure and chromosomal localization of Mylk.
AUTHOR: Giorgi D; Ferraz C; Mattei M G; Demaille J; Rouquier S
CORPORATE SOURCE: IGH, CNRS UPR 1142, rue de la Cardonille, 34396 Montpellier, Cedex 5, France.
SOURCE: Genomics, (2001 Jul) 75 (1-3) 49-56.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF335470
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB The gene encoding **myosin light chain kinase** (MYLK) is duplicated on **human** chromosome 3 (HSA3; 3p13;3q21) and on a chromosome with conserved synteny to HSA3 in most non-**human** primate species. In **human**, the functional copy resides on 3q21, whereas the 3p13 site contains a pseudogene. To trace the origin of the duplication, we characterized the mouse gene Mylk. A single sequence corresponding to the functional Mylk was detected. We sequenced a 180-kb bacterial artificial chromosome **clone** containing the 24 first exons of Mylk; the complete mouse gene is expected to span >200 kb. Comparisons with the draft of the **human** genome revealed that the sequence and structure of MYLK are conserved in mammals. Fluorescence in situ hybridization (FISH) analysis indicated that the mouse gene localizes to a single site on chromosome 16B4-B5, a region with conserved synteny with HSA3q. Our study provides information on both the structure and the evolution of MYLK in mammals and suggests that it was duplicated after the divergence of rodents and primates.

L10 ANSWER 51 OF 93 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001082718 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10973969
TITLE: Striated muscle preferentially **expressed** genes alpha and beta are two serine/threonine protein **kinases** derived from the same gene as the aortic preferentially **expressed** gene-1.
AUTHOR: Hsieh C M; Fukumoto S; Layne M D; Maemura K; Charles H; Patel A; Perrella M A; Lee M E
CORPORATE SOURCE: Cardiovascular and the Pulmonary and Critical Care Divisions, Brigham and Women's Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: GM53249 (NIGMS)
HL10113 (NHLBI)
HL60788 (NHLBI)
SOURCE: Journal of biological chemistry, (2000 Nov 24) 275 (47) 36966-73.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF215896
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010108

AB Aortic preferentially **expressed** gene (APEG)-1 is a 1.4-kilobase pair (kb) mRNA **expressed** in vascular smooth muscle cells and is down-regulated by vascular injury. An APEG-1 5'-end cDNA probe identified three additional isoforms. The 9-kb striated preferentially **expressed** gene (SPEG)alpha and the 11-kb SPEGbeta were found in skeletal muscle and heart. The 4-kb brain preferentially **expressed** gene was detected in the brain and aorta. We report here **cloning** of the 11-kb SPEGbeta cDNA. SPEGbeta encodes a 355-kDa protein that contains two serine/threonine **kinase** domains and is **homologous** to proteins of the **myosin light chain kinase** family. At least one **kinase** domain is active and capable of autophosphorylation. In the genome, all four isoforms share the middle three of the five exons of

APEG-1, and they differ from each other by using different 5'- and 3'-ends and alternative splicing. We show that the **expression** of SPEGalpha and SPEGbeta is developmentally regulated in the striated muscle during C2C12 myoblast to myotube differentiation in vitro and cardiomyocyte maturation in vivo. This developmental regulation suggests that both SPEGalpha and SPEGbeta can serve as sensitive markers for striated muscle differentiation and that they may be important for adult striated muscle function.

L10 ANSWER 52 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2001074385 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10926933
TITLE: An extended conformation of calmodulin induces interactions between the structural domains of adenylyl cyclase from Bacillus anthracis to promote catalysis.
AUTHOR: Drum C L; Yan S Z; Sarac R; Mabuchi Y; Beckingham K; Bohm A; Grabarek Z; Tang W J
CORPORATE SOURCE: Department of Neurobiology, Pharmacology, and Physiology, University of Chicago, Chicago, Illinois 60637, USA.
CONTRACT NUMBER: AR41637 (NIAMS)
DA05778 (NIDA)
GM53459 (NIGMS)
SOURCE: Journal of biological chemistry, (2000 Nov 17) 275 (46) 36334-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020420
Entered Medline: 20001229

AB The edema factor exotoxin produced by Bacillus anthracis is an adenylyl cyclase that is activated by calmodulin (CaM) at resting state calcium concentrations in infected cells. A C-terminal 60-kDa fragment corresponding to the catalytic domain of edema factor (EF3) was **cloned**, overexpressed in Escherichia coli, and purified. The N-terminal 43-kDa domain (EF3-N) of EF3, the sole domain of edema factor **homologous** to adenylyl cyclases from Bordetella pertussis and Pseudomonas aeruginosa, is highly resistant to protease digestion. The C-terminal 160-amino acid domain (EF3-C) of EF3 is sensitive to proteolysis in the absence of CaM. The addition of CaM protects EF3-C from being digested by proteases. EF3-N and EF3-C were **expressed** separately, and both fragments were required to reconstitute full CaM-sensitive enzyme activity. Fluorescence resonance energy transfer experiments using a double-labeled CaM molecule were performed and indicated that CaM adopts an extended conformation upon binding to EF3. This contrasts sharply with the compact conformation adopted by CaM upon binding **myosin light chain kinase** and CaM-dependent protein **kinase** type II. Mutations in each of the four calcium binding sites of CaM were examined for their effect on EF3 activation. Sites 3 and 4 were found critical for the activation, and neither the N- nor the C-terminal domain of CaM alone was capable of activating EF3. A genetic screen probing loss-of-function mutations of EF3 and site-directed mutations based on the **homology** of the edema factor family revealed a conserved pair of aspartate residues and an arginine that are important for catalysis. Similar residues are essential for di-metal-mediated catalysis in mammalian adenylyl cyclases and a family of DNA polymerases and nucleotidyltransferases. This suggests that edema factor may utilize a similar catalytic mechanism.

L10 ANSWER 53 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2000304927 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10844022
TITLE: Interaction of the postsynaptic density-95/guanylate **kinase** domain-associated protein complex with a light chain of myosin-V and dynein.
AUTHOR: Naisbitt S; Valtschanoff J; Allison D W; Sala C; Kim E; Craig A M; Weinberg R J; Sheng M
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Neurobiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.
CONTRACT NUMBER: NS29879 (NINDS)
NS33184 (NINDS)
NS35050 (NINDS)
SOURCE: Journal of neuroscience : official journal of the Society for Neuroscience, (2000 Jun 15) 20 (12) 4524-34.
Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB NMDA receptors interact directly with postsynaptic density-95 (PSD-95), a scaffold protein that organizes a cytoskeletal- signaling complex at the postsynaptic membrane. The molecular mechanism by which the PSD-95-based protein complex is trafficked to the postsynaptic site is unknown but presumably involves specific motor proteins. Here we demonstrate a direct interaction between the PSD-95-associated protein guanylate **kinase** domain-associated protein (GKAP) and dynein light chain (DLC), a light chain subunit shared by myosin-V (an actin-based motor) and cytoplasmic dynein (a microtubule-based motor). A yeast two-hybrid screen with GKAP isolated DLC2, a novel protein 93% identical to the previously **cloned** 8 kDa dynein light chain (DLC1). A complex containing PSD-95, GKAP, DLC, and myosin-V can be immunoprecipitated from rat brain extracts. DLC colocalizes with PSD-95 and F-actin in dendritic spines of cultured neurons and is enriched in biochemical purifications of PSD. Immunogold electron microscopy reveals a concentration of DLC in the postsynaptic compartment of asymmetric synapses of brain in which it is associated with the PSD and the spine apparatus. We discuss the possibility that the GKAP/DLC interaction may be involved in trafficking of the PSD-95 complex by motor proteins.

L10 ANSWER 54 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2000092896 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10625668
TITLE: Requirement of calmodulin binding by HIV-1 gp160 for enhanced FAS-mediated apoptosis.
AUTHOR: Micoli K J; Pan G; Wu Y; Williams J P; Cook W J; McDonald J M
CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.
CONTRACT NUMBER: CA/72823 (NCI)
SOURCE: Journal of biological chemistry, (2000 Jan 14) 275 (2) 1233-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000218

AB Accelerated apoptosis is one mechanism proposed for the loss of CD4+ T-lymphocytes in **human** immunodeficiency virus type 1 (HIV-1) infection. The HIV-1 envelope glycoprotein, gp160, contains two C-terminal calmodulin-binding domains. **Expression** of gp160 in Jurkat T-cells results in increased sensitivity to FAS- and ceramide-mediated apoptosis. The pro-apoptotic effect of gp160 **expression** is blocked by two calmodulin antagonists, tamoxifen and trifluoperazine. This enhanced apoptosis in response to FAS antibody or C(2)-ceramide is associated with activation of caspase 3, a critical mediator of apoptosis. A point mutation in the C-terminal calmodulin-binding domain of gp160 (alanine 835 to tryptophan, A835W) eliminates gp160-dependent enhanced FAS-mediated apoptosis in transiently transfected cells, as well as in vitro calmodulin binding to a peptide corresponding to the C-terminal calmodulin-binding domain of gp160. Stable Tet-off Jurkat cell lines were developed that inducibly **express** wild type gp160 or gp160A835W. Increasing **expression** of wild type gp160, but not gp160A835W, correlates with increased calmodulin levels, increased apoptosis, and caspase 3 activation in response to anti-FAS treatment. The data indicate that gp160-enhanced apoptosis is dependent upon calmodulin up-regulation, involves the activation of caspase 3, and requires calmodulin binding to the C-terminal binding domain of gp160.

L10 ANSWER 55 OF 93 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel serine/threonine **kinase** involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: Molecular and cellular biology, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase** -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine **kinase** which shows high degree of **homology** to DAP **kinase**. The region of **homology** spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP **kinase** and displays no **homology** to any known protein. The catalytic domain is also **homologous** to the recently identified ZIP **kinase** and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel **subfamily** of serine/threonine **kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the **myosin light chain**, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active **kinase**. Ectopically **expressed** DRP-1 induced apoptosis in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of

the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death domain was found to block apoptosis induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L10 ANSWER 56 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2000444850 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10992197
TITLE: Genetic **expression** by fetal chorionic villi during the first trimester of **human** gestation.
AUTHOR: Dizon-Townson D S; Lu J; Morgan T K; Ward K J
CORPORATE SOURCE: Departments of Obstetrics and Gynecology and Human Genetics, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.
SOURCE: American journal of obstetrics and gynecology, (2000 Sep) 183 (3) 706-11.
Journal code: 0370476. ISSN: 0002-9378.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001010

AB OBJECTIVE: The growth and differentiation of the embryo and the contiguous placental structures are fundamental to **human** reproduction and survival. Little is known, however, about the genetic control of these processes during early **human** development. Normal placentation is the result of a well-orchestrated sequence of events that consists of cellular adhesion and limited invasion controlled by relatively unknown genetic processes. We hypothesized that genes **expressed** by first-trimester chorionic villi constitute critical regulators of placentation and hence of early **human** development. Our objective was therefore to isolate and characterize genes, both known and unknown, **expressed** by the **human** placenta during the first trimester. STUDY DESIGN: Tissues collected consisted of placental material collected during first-trimester elective pregnancy terminations. Fetal chorionic villi were separated grossly from maternal decidual and quickly frozen in liquid nitrogen for ribonucleic acid preservation. Tissues from different gestational ages were kept separate. Total ribonucleic acid was extracted, messenger ribonucleic acid was isolated, and complementary deoxyribonucleic acid was synthesized. Complementary deoxyribonucleic acid was **cloned** into the ZAP **Express** lambda vector (Stratagene, La Jolla, Calif). Automated sequencing of random plaques was done. Sequence **homology** was searched for with the Basic Local Assignment Search Tool to search the Genbank database (National Center for Biotechnology Institute, Bethesda, Md). In the event that a known gene sequence was derived, no further workup was undertaken. If no **homology** was identified, the complete complementary deoxyribonucleic acid insert was sequenced in its entirety. Novel genes were further characterized by tissue-specific patterns, cellular localization, and chromosomal location. **Expression** by fetal villi was confirmed by reverse transcriptase polymerase chain reaction. RESULTS: We isolated a number of genes known to be **expressed** at the maternal-fetal interface. Seventeen of 186 random **clones** were >1 kilobase in length and did not display **homology** with known genes, and these may therefore constitute novel genes critical for placentation. One of the **clones** from a **human**

chorionic villi complementary deoxyribonucleic acid library at 12 weeks' gestation is a 7-kilobase gene that is also abundantly **expressed** in **human** fetal brain, lung, liver, and kidney. In situ hybridization localized the transcript to the fetal renal glomerulus. CONCLUSIONS: Our findings indicate that the placenta serves as a rich source for potential novel gene **expression**. Seventeen **clones** were >1 kilobase in length and are potential novel genes involved in early first-trimester placentation. One of these 17 potential novel genes is **expressed** in abundance in several fetal tissues, which suggests a role in early **human** fetal development. Other potential novel genes are currently being characterized. The powerful molecular techniques that we used to isolate genes **expressed** by early fetal chorionic villi will lead us to a better understanding of the genetic control of normal **human** reproduction. They also may be used to study obstetric and other **human** disease.

L10 ANSWER 57 OF 93 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2000175199 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10708550
TITLE: Up-regulation of p21- and RhoA-activated protein **kinases** in **human** pregnant myometrium.
AUTHOR: Moore F; Da Silva C; Wilde J I; Smarason A; Watson S P; Lopez Bernal A
CORPORATE SOURCE: Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom.
SOURCE: Biochemical and biophysical research communications, (2000 Mar 16) 269 (2) 322-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000419

AB The role of small ras **homologous** GTP-binding proteins in the regulation of smooth muscle contractility has become increasingly apparent but there is still little information about the presence of these proteins in **human** uterine smooth muscle. Messenger RNAs for p21-activated protein **kinase** isoforms (PAK1, PAK2, and PAK3) were detectable in both nonpregnant and pregnant **human** myometrial tissue. However, PAK3 protein was not detectable and the proteins for PAK1 and PAK2 were only detectable in pregnant tissue. Moreover there was a large increase in the constitutively active p34 protein fragment of PAK2 in pregnant tissue. Protein **expression** of RhoA-activated protein **kinases** isoforms (ROK1 and ROK2) also increased during pregnancy. Stimulation of RhoA signaling in pregnant myometrial tissue with lysophosphatic acid (LPA) increased the level of **myosin light chain** (MLC20) phosphorylation. Preincubation of the tissue with C3 toxin inhibited LPA-stimulated MLC20 phosphorylation and lowered the basal phosphorylation level of MLC20. Thus ROKS and PAKS have the potential to regulate uterine contractility and/or load-bearing during **human** pregnancy.

L10 ANSWER 58 OF 93 EMBASE
on STN DUPLICATE 12
ACCESSION NUMBER: 2000105458 EMBASE
TITLE: Characterization of the **human** herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) oncogene, Kaposin (ORF K12).
AUTHOR: Muralidhar S.; Veytsmann G.; Chandran B.; Ablashi D.;

Doniger J.; Rosenthal L.J.
CORPORATE SOURCE: L.J. Rosenthal, Dept. of Microbiology/Immunology, Georgetown University, Medical Center, 3900 Reservoir Road N.W., Washington, DC 20007, United States. rosenthl@gunet.georgetown.edu
SOURCE: Journal of Clinical Virology, (2000) 16/3 (203-213). Refs: 58
ISSN: 1386-6532 CODEN: JCVIFB
PUBLISHER IDENT.: S 1386-6532(99)00081-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
004 Microbiology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: **Human** herpesvirus 8 (HHV-8) has been implicated in the etiology of Kaposi's sarcoma (KS), a highly angiogenic tumor of complex histology, and two lymphoproliferative diseases, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). A number of HHV-8 encoded genes have been proposed to be involved in the pathogenesis of KS and PEL and a few have been shown to be oncogenic in heterologous systems (Reyes GR, LaFemina R, Hayward SD, Hayward GS. Morphological transformation by DNA fragments of **human** herpesviruses: evidence for two distinct transforming regions in herpes simplex virus types 1 and 2 and lack of correlation with biochemical transfer of the thymidine **kinase** gene. Cold Spring Harbor Symp Quant Biol 1980;44:629-641; Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of **human** cytokine and cytokine response pathway genes by KSHV. Science 1996;274:1739-1744; Cheng EH, Nicholas J, Bellows DS, Hayward GS, Guo HG, Reitz MS, Hardwick JM. A Bcl-2 **homolog** encoded by Kaposi sarcoma-associated virus, **human** herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. Proc Natl Acad Sci USA 1997;94:690-694; Li M, Lee H, Yoon DW, Albrecht JC, Fleckenstein B, Neipel F, Jung JU. Kaposi's sarcoma-associated herpesvirus encodes a functional cyclin. J Virol 1997;71:1984-1991; Neipel F, Albrecht J-C, Fleckenstein B. Cell-**homologous** genes In the Kaposi's sarcoma-associated rhadinovirus **human** herpesvirus 8: determinants of its pathogenicity? J Virol 1997;71:4187-4192; Nicholas J, Ruvolo VR, Burns WH, Sandford G, Wan X, Ciufo D, Hendrickson SB, Guo HG, Hayward GS, Reitz MS. Kaposi's sarcoma-associated **human** herpesvirus-8 encodes **homologues** of macrophage inflammatory protein-1 and interleukin-6. Nat Med 1997;3:287-292; Nicholas J, Zong J, Alcendor DJ, Ciufu DM, Poole LJ, Sarisky RT, Chiuo C, Zhang X, Wan X, Guo H, Reitz MS, Hayward GS. Novel organizational features, captured cellular genes, and strain variability within the genome of KSHV/HHV-8. JNCI Monographs 1998;23:79-88; Muralidhar S, Pumfery AM, Hassani M, Sadaie MR, Azumi N, Kishishita M, Brady JN, Doniger J, Medveczky P, Rosenthal LJ. Identification of kaposin (ORF K12) as a **human** herpesvirus 8 (Kaposi's sarcoma associated herpesvirus) transforming gene. J Virol 1998;72:4980-4988). The kaposin gene (ORF K12) encoded by the abundant latency-associated HHV-8 transcript, T0.7, has been previously shown to induce tumorigenic transformation of Rat-3 cells (Muralidhar S, Pumfery AM, Hassani M, Sadaie MR, Azumi N, Kishishita M, Brady JN, Doniger J, Medveczky P, Rosenthal LJ. Identification of kaposin (ORF K12) as a **human** herpesvirus 8 (Kaposi's sarcoma associated herpesvirus) transforming gene. J Virol 1998;72:4980-4988). The current study is a further characterization of kaposin protein. Objectives: Characterization of kaposin **expression** in transformed and tumor-derived Rat-3 cells as well as PEL cell lines, BCBL-1, BC-3 and KS-1 and analysis of mechanism(s) of transformation. Design: The presence of kaposin DNA in transformed cells was determined by fluorescent in situ hybridization (FISH). **Expression** of kaposin protein was analyzed by Western

blot analysis and indirect immunofluorescence assay (IFA). Activation of cellular **kinases** in kaposin-transformed cells was analyzed using Phosphospot peptide strips (Jerini Biotools). Results: Kaposin DNA was integrated at a single locus in the genome of transformed Rat-3 cells as determined by FISH. Kaposin protein was **expressed** predominantly in the cytoplasm and colocalized with the 58 kDa Golgi membrane protein in transformed Rat-3 cells. Western blot analysis of transformed Rat-3 cells revealed predominant protein bands of approximately 16-18 kDa. Predominant 16-18 kDa bands were also detected in PEL cell lines BCBL-1, BC-3 and KS-1. In addition, bands of higher molecular weight were detected in both transformed Rat-3 cells and PEL cells. Kaposin-transformed Rat-3 cells showed a 3-fold increase in the activities of serine-threonine **kinases** such as protein **kinase** C (PKC), calcium/calmodulin-dependent **kinase** II (CAM **kinase** II) and **myosin light chain kinase** (**MLCK**). In addition, a 2-fold increase in the activities of Cdc2-**kinase** and cyclic-GMP (c-GMP)-dependent protein **kinase** was also observed. Conclusions: Results indicated that kaposin DNA was retained in transformed Rat-3 cells and **expressed** as predominantly cytoplasmic proteins of 16-18 kDa. Importantly, kaposin protein **expression** was detected by Western blot analysis in PEL cell lines, BCBL-1, BC-3 and KS-1. Preliminary studies indicated that kaposin may be involved in the activation of cellular serine-threonine **kinases** which play an important role in cell proliferation such as PKC, CAM **kinase** II and cdc2-**kinase**.

L10 ANSWER 59 OF 93 EMBASE on STN

ACCESSION NUMBER: 2000349664 EMBASE

TITLE: c-Kit and c-kit mutations in mastocytosis and other hematological diseases.

AUTHOR: Boissan M.; Feger F.; Guillosson J.-J.; Arock M.

CORPORATE SOURCE: Prof. M. Arock, Cellular/Molecular Hematology Unit, UPRES EA 2509, Faculty of Pharmacy, 4 Ave. de l'Observatoire, 75006 Paris, France. michel.arock@psl.ap-hop-paris.fr

SOURCE: Journal of Leukocyte Biology, (2000) 67/2 (135-148).
Refs: 129
ISSN: 0741-5400 CODEN: JLBIE7

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 022 Human Genetics
025 Hematology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Mast cells (MC) are tissue elements derived from hematopoietic stem cells. Their differentiation and proliferation processes are under the influence of cytokines, including one of utmost importance known as stem cell factor (SCF). SCF receptor is encoded by the protooncogene c-kit, belongs to the type III receptor tyrosine **kinase subfamily**, and is also **expressed** on other hematopoieric or non-hematopoietic cells. Ligation of c-kit receptor by SCF induces its dimerization, followed by induction of multiple intracelluar signaling pathways leading to cell proliferatlon and activation. Mastocytosis, a relatively rare group of diseases characterized by accumulation of MC in various tissues, are found isolated or sometimes associated with other hematological malignancies in **humans**. Although the initial events leading to mastocytosis are not yet unraveled, alterations of the c-kit gene have been described. Particularly interesting are acquired mutations resulting in a constitutively activated receptor, possibly involved in the increased numbers of MC in tissues. For this reason, future strategies might be envisaged to target specifically the mutated c-kit and/or its intracellular signaling.

L10 ANSWER 60 OF 93 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2000472776 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10906760
TITLE: Characterization of the protein phosphatase 1 catalytic subunit in endothelium: involvement in contractile responses.
AUTHOR: Verin A D; Csortos C; Durbin S D; Aydanyan A; Wang P; Patterson C E; Garcia J G
CORPORATE SOURCE: Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21224, USA.. averin@welch.jhu.edu
CONTRACT NUMBER: HL50533 (NHLBI)
HL57402 (NHLBI)
HL58064 (NHLBI)
SOURCE: Journal of cellular biochemistry, (2000 Jul 19) 79 (1) 113-25.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20000929

AB We have previously demonstrated the direct involvement of a type 1 Ser/Thr phosphatase (PPase 1) in endothelial cell (EC) barrier regulation [Am. J. Physiol. 269:L99-L108, 1995]. To further extend this observation, we microinjected either the Ser/Thr PPase inhibitor, calyculin, or the PPase 1 inhibitory protein, I-2 into bovine pulmonary artery EC and demonstrated both an increase in F-actin stress fibers and a shift from a regular polygonal shape to a spindle shape with gaps apparent at the cell borders. Northern blot analysis with specific cDNA probes revealed the presence of three major PPase 1 catalytic subunit (CS1) isoforms (alpha, delta, and gamma) in **human** and bovine EC. To characterize the myosin-associated EC CS1 isoform, myosin-enriched bovine EC fraction was screened with anti-CS1alpha and anti-CS1delta antibodies The anti-CS1delta antiserum, but not anti-CS1alpha antiserum cross reacts with the CS1 isoform present in myosin-enriched fraction and CS1delta was found in stable association with EC myosin/**myosin light chain kinase** (**MLCK**) complex in **MLCK** immunoprecipitates under nondenaturing conditions. Consistent with these data, overexpression of CS1delta-GFP construct in bovine endothelium followed by immunoprecipitation of CS1 with anti-GFP antibody revealed the stable association of CS1delta with actomyosin complex. Finally, screening of a **human** EC oligo(dT)-primed cDNA library with a probe encoding a rat CS1delta cDNA segment yielding several positive **clones** that encoded the entire CS1delta open reading frame and partially noncoding regions. Sequence analysis determined a high **homology** (approximately 99%) with **human** CS1delta derived from a teratocarcinoma cell line. Together, these data suggest that CS1delta is the major of PPase 1 isoform specifically associated with EC actomyosin complex and which participates in EC barrier regulation.

L10 ANSWER 61 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:376177 HCAPLUS
DOCUMENT NUMBER: 133:248010
TITLE: Identification of differentially **expressed** genes in cardiac hypertrophy by analysis of **expressed** sequence tags
AUTHOR(S): Hwang, David M.; Dempsey, Adam A.; Lee, Cheuk-Yu; Liew, Choong-Chin
CORPORATE SOURCE: Cardiac Gene Unit, Department of Laboratory Medicine

and Pathobiology, Centre for Cardiovascular Research, Toronto Hospital, University of Toronto, Toronto, ON, M5G 1L5, Can.
SOURCE: Genomics (2000), 66(1), 1-14
CODEN: GNMCEP; ISSN: 0888-7543
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cardiac hypertrophy is an adaptive response to chronic hemodynamic overload. We employed a whole-genome approach using **expressed** sequence tags (ESTs) to characterize gene transcription and identify new genes overexpressed in cardiac hypertrophy. Anal. of general transcription patterns revealed a proportional increase in transcripts related to cell/organism defense and a decrease in transcripts related to cell structure and motility in hypertrophic hearts compared to normal hearts. Detailed comparison of individual gene **expression** identified 64 genes potentially overexpressed in hypertrophy, of 232 candidate genes derived from a set of 77,692 cardiac ESTs, including 47,856 ESTs generated in our laboratory Of these, 29 were good candidates ($P < 0.0002$) and 35 were weaker candidates ($P < 0.005$). RT-PCR of a number of these candidate genes demonstrated correspondence of EST-based predictions of gene **expression** with in vitro levels. Consistent with an organ under various stresses, up to one-half of the good candidates predicted to exhibit differential **expression** were genes potentially involved in stress response. Analyses of general transcription patterns and of single-gene **expression** levels were also suggestive of increased protein synthesis in the hypertrophic myocardium. Overall, these results depict a scenario compatible with current understanding of cardiac hypertrophy. However, the identification of several genes not previously known to exhibit increased **expression** in cardiac hypertrophy (e.g., prostaglandin D synthases; CD59 antigen) also suggests a number of new avenues for further investigation. These data demonstrate the utility of genome-based resources for investigating questions of cardiovascular biol. and medicine. (c) 2000 Academic Press.
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 62 OF 93 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:955377 SCISEARCH
THE GENUINE ARTICLE: 263HN
TITLE: Interaction partners of Dlk/ZIP **kinase**: co-**expression** of Dlk/ZIP **kinase** and Par-4 results in cytoplasmic retention and apoptosis
AUTHOR: Page G; Kogel D; Rangnekar V; Scheidtmann K H (Reprint)
CORPORATE SOURCE: UNIV BONN, INST GENET, ROEMERSTR 164, D-53117 BONN, GERMANY (Reprint); UNIV BONN, INST GENET, D-53117 BONN, GERMANY; UNIV KENTUCKY, LEXINGTON, KY 40536
COUNTRY OF AUTHOR: GERMANY; USA
SOURCE: ONCOGENE, (2 DEC 1999) Vol. 18, No. 51, pp. 7265-7273. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0950-9232.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 48
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Dlk/ZIP **kinase** is a newly discovered serine/threonine **kinase** which, due to its **homology** to DAP **kinase**, was named DAP like **kinase**, Dlk, This **kinase** is tightly associated with nuclear structures, it undergoes extensive autophosphorylation and phosphorylates **myosin light chain** and core histones H3, H2A and H4 in vitro. Moreover, it

possesses a leucine zipper which mediates interaction with transcription factor ATF-4, therefore it was called ZIP **kinase**, We employed the yeast two-hybrid system to identify interaction partners of Dlk that might serve as regulators or targets. Besides ATF-4 and others we found Par-4, a modulator of transcription factor WT1 and mediator of apoptosis. Complex formation between Dlk and Par-4 was confirmed by GST pull-down experiments and **kinase** reactions ill vitro and coexpression experiments in vivo. The interaction domain within Dlk was mapped to an arginine-rich region between residues 338-417, rather than to the leucine zipper. Strikingly, coexpression of Dlk and Par-4 lead to relocation of Dlk from the nucleus to the cytoplasm, particularly to actin filaments. These interactions provoked a dramatic reorganization of the cytoskeleton and morphological symptoms of apoptosis, thus suggesting a functional relationship between Dlk and Par-4 in the control of apoptosis.

L10 ANSWER 63 OF 93 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1999303018 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10376525
TITLE: Death-associated protein **kinase** 2 is a new calcium/calmodulin-dependent protein **kinase** that signals apoptosis through its catalytic activity.
AUTHOR: Kawai T; Nomura F; Hoshino K; Copeland N G; Gilbert D J; Jenkins N A; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, Nishinomiya, Japan.
SOURCE: Oncogene, (1999 Jun 10) 18 (23) 3471-80.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB018001; GENBANK-AB018002
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990630

AB We have identified and characterized a new calcium/calmodulin (Ca2+/CaM) dependent protein **kinase** termed death-associated protein **kinase** 2 (DAPK2) that contains an N-terminal protein **kinase** domain followed by a conserved CaM-binding domain with significant **homologies** to those of DAP **kinase**, a protein **kinase** involved in apoptosis. DAPK2 mRNA is **expressed** abundantly in heart, lung and skeletal muscle. The mapping results indicated that DAPK2 is located in the central region of mouse chromosome 9. In vitro **kinase** assay revealed that DAPK2 is autophosphorylated and phosphorylates **myosin light chain** (MLC) as an exogenous substrate. DAPK2 binds directly to CaM and is activated in a Ca2+/CaM-dependent manner. A constitutively active DAPK2 mutant is generated by removal of the CaM-binding domain (deltaCaM). Treatment of agonists that elevate intracellular Ca2+-concentration led to the activation of DAPK2 and transfection studies revealed that DAPK2 is localized in the cytoplasm. Overexpression of DAPK2, but not the **kinase** negative mutant, significantly induced the morphological changes characteristic of apoptosis. These results indicate that DAPK2 is an additional member of DAP **kinase** family involved in apoptotic signaling.

L10 ANSWER 64 OF 93 MEDLINE on STN
ACCESSION NUMBER: 1999230348 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10212154
TITLE: Regulatory light chain mutations affect myosin motor function and kinetics.
AUTHOR: Chaudoir B M; Kowalczyk P A; Chisholm R L
CORPORATE SOURCE: Dept of Cell and Molecular Biology, Northwestern University

Medical School, Ward 11-100, Chicago, IL 60611-3008, USA.
CONTRACT NUMBER: GM39264 (NIGMS)
SOURCE: Journal of cell science, (1999 May) 112 (Pt 10) 1611-20.
Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990813

AB The actin-based motor protein myosin II plays a critical role in many cellular processes in both muscle and non-muscle cells. Targeted disruption of the Dictyostelium regulatory light chain (RLC) caused defects in cytokinesis and multicellular morphogenesis. In contrast, a myosin heavy chain mutant lacking the RLC binding site, and therefore bound RLC, showed normal cytokinesis and development. One interpretation of these apparently contradictory results is that the phenotypic defects in the RLC null mutant results from mislocalization of myosin caused by aggregation of RLC null myosin. To distinguish this from the alternative explanation that the RLC can directly influence myosin activity, we **expressed** three RLC point mutations (E12T, G18K and N94A) in a Dictyostelium RLC null mutant. The position of these mutations corresponds to the position of mutations that have been shown to result in familial hypertrophic cardiomyopathy in **humans**. Analysis of purified Dictyostelium myosin showed that while these mutations did not affect binding of the RLC to the MHC, its phosphorylation by **myosin light chain kinase** or regulation of its activity by phosphorylation, they resulted in decreased myosin function. All three mutants showed impaired cytokinesis in suspension, and one produced defective fruiting bodies with short stalks and decreased spore formation. The abnormal myosin localization seen in the RLC null mutant was restored to wild-type localization by **expression** of all three RLC mutants. Although two of the mutant myosins had wild-type actin-activated ATPase, they produced in vitro motility rates half that of wild type. N94A myosin showed a fivefold decrease in actin-ATPase and a similar decrease in the rate at which it moved actin in vitro. These results indicate that the RLC can play a direct role in determining the force transmission and kinetic properties of myosin.

L10 ANSWER 65 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2000035748 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10570971
TITLE: Identification and characterization of Drosophila **homolog** of Rho-**kinase**.
AUTHOR: Mizuno T; Amano M; Kaibuchi K; Nishida Y
CORPORATE SOURCE: Division of Biological Science, Graduate School of Science, Nagoya University, Japan.
SOURCE: Gene, (1999 Oct 1) 238 (2) 437-44.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF151375
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991202

AB The Rho family of small GTPases and their associated regulators and targets are essential mediators of diverse morphogenetic events in development. Mammalian Rho-**kinase**/ROK alpha, one of the targets

of Rho, has been shown to bind to Rho in GTP-bound form and to phosphorylate the **myosin light chain** (MLC) and the myosin-binding subunit (MBS) of myosin phosphatase, resulting in the activation of myosin. Thus, Rho-**kinase**/ROK alpha has been suggested to play essential roles in the formation of stress fibers and focal adhesions. We have identified the Drosophila **homolog** of Rho-**kinase**/ROK alpha, DRho-**kinase**, which has conserved the basic structural feature of Rho-**kinase**/ROK alpha consisting of the N-terminal **kinase**, central coiled-coil and C-terminal pleckstrin **homology** (PH) domains. A two-hybrid analysis demonstrated that DRho-**kinase** interacts with the GTP-bound form of the Drosophila Rho. Drho1, at the conserved Rho-binding site. DRho-**kinase** can phosphorylate MLC and MBS, preferable substrates for bovine Rho-**kinase**, in vitro. DRho-**kinase** is ubiquitously **expressed** throughout development, in a pattern essentially identical to that of Drho1. These results suggest that DRho-**kinase** is an effector of Drho1.

L10 ANSWER 66 OF 93 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1999216425 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10198171
TITLE: **Cloning** and chromosomal localization of **human** Cdc42-binding protein **kinase** beta.
AUTHOR: Moncrieff C L; Bailey M E; Morrison N; Johnson K J
CORPORATE SOURCE: Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, G11 6NU.
SOURCE: Genomics, (1999 Apr 15) 57 (2) 297-300.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF128625
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990506

AB The p21 GTPases, Rho and Cdc42, regulate numerous cellular functions by binding to members of a serine/threonine protein **kinase subfamily**. These functions include the remodeling of the cell cytoskeleton that is a feature of cell growth and differentiation. Two of these p21 GTPase-regulated **kinases**, the myotonic dystrophy protein **kinase**-related Cdc42-binding **kinases** (MRCKalpha and beta), have been recently characterized in rat. Both of these proteins phosphorylate nonmuscle **myosin light chain**, a prerequisite for the activation of actin-myosin contractility. Here we report the cDNA **cloning** of the **human homologue** of MRCKbeta, CDC42BPB, which was found by Northern blot analysis to be **expressed** in a wide range of tissues. The **human** CDC42BPB gene maps to cytogenetic band 14q32.3 by FISH analysis.

L10 ANSWER 67 OF 93 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 1999216419 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10198165
TITLE: A single **human myosin light chain kinase** gene (**MLCK**; MYLK).
AUTHOR: Lazar V; Garcia J G
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21224, USA.
CONTRACT NUMBER: HL 50533 (NHLBI)
HL 58064 (NHLBI)

SOURCE: Genomics, (1999 Apr 15) 57 (2) 256-67.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990506

AB The **myosin light chain kinase** (**MLCK**) gene, a muscle member of the immunoglobulin gene superfamily, yields both smooth muscle and nonmuscle cell isoforms. Both isoforms are known to regulate contractile activity via calcium/calmodulin-dependent **myosin light chain** phosphorylation. We previously **cloned** from a **human** endothelial cell (EC) cDNA library a high-molecular-weight nonmuscle **MLCK** isoform (EC **MLCK** (**MLCK** 1) with an open reading frame that encodes a protein of 1914 amino acids. We now describe four novel nonmuscle **MLCK** isoforms (**MLCK** 2, 3a, 3b, and 4) that are the alternatively spliced variants of an mRNA precursor that is transcribed from a single **human MLCK** gene. The primary structure of the cDNA encoding the nonmuscle **MLCK** isoform 2 is identical to the previously published **human** nonmuscle **MLCK** (**MLCK** 1) (J. G. N. Garcia et al., 1997, Am. J. Respir. Cell Mol. Biol. 16, 489-494) except for a deletion of nucleotides 1428-1634 (D2). The full nucleotide sequence of **MLCK** isoforms 3a and 3b and partial sequence for **MLCK** isoform 4 revealed identity to **MLCK** 1 except for deletions at nucleotides 5081-5233 (**MLCK** 3a, D3), double deletions of nucleotides 1428-1634 and 5081-5233 (**MLCK** 3b), and nucleotide deletions 4534-4737 (**MLCK** 4, D4). Northern blot analysis demonstrated the extended **expression** pattern of the nonmuscle **MLCK** isoform(s) in both **human** adult and **human** fetal tissues. RT-PCR using primer pairs that were designed to detect specifically nonmuscle **MLCK** isoforms 2, 3, and 4 deletions (D2, D3, and D4) confirmed **expression** in both **human** adult and **human** fetal tissues (lung, liver, brain, and kidney) and in **human** endothelial cells (umbilical vein and dermal). Furthermore, relative quantitative **expression** studies demonstrated that the nonmuscle **MLCK** isoform 2 is the dominant splice variant **expressed** in **human** tissues and cells. Further analysis of the **human MLCK** gene revealed that the **MLCK** 2 isoform represents the deletion of an independent exon flanked by 5' and 3' neighboring introns of 0.6 and 7.0 kb, respectively. Together these studies demonstrate for the first time that the **human MLCK** gene yields multiple nonmuscle **MLCK** isoforms by alternative splicing of its transcribed mRNA precursor with differential distribution of these isoforms in various **human** tissues and cells.

L10 ANSWER 68 OF 93 MEDLINE on STN
ACCESSION NUMBER: 1999003259 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9786912
TITLE: DRAKs, novel serine/threonine **kinases** related to death-associated protein **kinase** that trigger apoptosis.
AUTHOR: Sanjo H; Kawai T; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
SOURCE: Journal of biological chemistry, (1998 Oct 30) 273 (44) 29066-71.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981201

AB The present study describes the **cloning** of two novel serine/threonine **kinases** termed DRAK1 and DRAK2, whose catalytic domains are related to that of death-associated protein **kinase**, a serine/threonine **kinase** involved in apoptosis. Both DRAKs are composed of the N-terminal catalytic domain and the C-terminal domain that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous **expression**. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate **myosin light chain** as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of apoptosis in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L10 ANSWER 69 OF 93 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:765634 HCAPLUS
DOCUMENT NUMBER: 130:137555
TITLE: Cellular gene **expression** altered by **human** cytomegalovirus: global monitoring with oligonucleotide arrays
AUTHOR(S): Zhu, Hua; Cong, Jian-Ping; Mamtora, Gargi; Gingeras, Thomas; Shenk, Thomas
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Molecular Biology, Princeton University, Princeton, NJ, 08544, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(24), 14470-14475
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mechanistic insights to viral replication and pathogenesis generally have come from the anal. of viral gene products, either by studying their biochem. activities and interactions individually or by creating mutant viruses and analyzing their phenotype. Now it is possible to identify and catalog the host cell genes whose mRNA levels change in response to a pathogen. We have used DNA array technol. to monitor the level of ≈6,600 **human** mRNAs in uninfected as compared with **human** cytomegalovirus-infected cells. The level of 258 mRNAs changed by a factor of 4 or more before the onset of viral DNA replication. Several of these mRNAs encode gene products that might play key roles in virus-induced pathogenesis, identifying them as intriguing targets for further study.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 70 OF 93 MEDLINE on STN
ACCESSION NUMBER: 1998204887 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9535879
TITLE: Regulatory segments of Ca2+/calmodulin-dependent protein **kinases**.
AUTHOR: Zhi G; Abdullah S M; Stull J T
CORPORATE SOURCE: Department of Physiology, University of Texas Southwestern Medical Center, Dallas, Texas 75235, USA.

CONTRACT NUMBER: HL06296 (NHLBI)
HL26043 (NHLBI)
SOURCE: Journal of biological chemistry, (1998 Apr 10) 273 (15) 8951-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980514

AB Catalytic cores of skeletal and smooth muscle **myosin light chain kinases** and Ca2+/calmodulin-dependent protein **kinase** II are regulated intrasterically by different regulatory segments containing autoinhibitory and calmodulin-binding sequences. The functional properties of these regulatory segments were examined in chimeric **kinases** containing either the catalytic core of skeletal muscle **myosin light chain kinase** or Ca2+/calmodulin-dependent protein **kinase** II with different regulatory segments. Recognition of protein substrates by the catalytic core of skeletal muscle **myosin light chain kinase** was altered with the regulatory segment of protein **kinase** II but not with smooth muscle **myosin light chain kinase**. Similarly, the catalytic properties of the protein **kinase** II were altered with regulatory segments from either **myosin light chain kinase**. All chimeric **kinases** were dependent on Ca2+/calmodulin for activity. The apparent Ca2+/calmodulin activation constant was similarly low with all chimeras containing the skeletal muscle catalytic core. The activation constant was greater with chimeric **kinases** containing the catalytic core of Ca2+/calmodulin-dependent protein **kinase** II with its endogenous or **myosin light chain kinase** regulatory segments. Thus, heterologous regulatory segments affect substrate recognition and **kinase** activity. Furthermore, the sensitivity to calmodulin activation is determined primarily by the respective catalytic cores, not the calmodulin-binding sequences.

L10 ANSWER 71 OF 93 MEDLINE on STN
ACCESSION NUMBER: 1998213668 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9545376
TITLE: TAPASIN, DAXX, RGL2, HKE2 and four new genes (BING 1, 3 to 5) form a dense cluster at the centromeric end of the MHC.
AUTHOR: Herberg J A; Beck S; Trowsdale J
CORPORATE SOURCE: Human Immunogenetics Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London, U.K.
SOURCE: Journal of molecular biology, (1998 Apr 10) 277 (4) 839-57.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 20000303
Entered Medline: 19980526

AB TAPASIN, a gene recently shown to be required for antigen presentation through MHC class I molecules, is located 180 kbp centromeric of HLA-DP in a region linked to several diseases, and associated with altered developmental phenotypes in the mouse. We present the genomic analysis of a 70 kbp gene-dense segment flanking the TAPASIN locus, including

sequence, structure and preliminary characterisation of seven additional genes. BING1 is a Zn finger gene containing a POZ motif. BING3 is similar to myosin regulatory light chain. BING4 shows **homologies** only to hypothetical yeast and Caenorhabditis elegans proteins. BING5 is found within an intron of BING4 on the complementary strand, and encodes a molecule with no **homologies** to database proteins. Another three genes were identified whose full sequence was not previously known; namely, RGL2, DAXX (BING2) and HKE2. RGL2 encodes an effector of Ras, **homologous** to the mouse RalGDS protein, Rlf. DAXX encodes an effector of Fas that stimulates apoptosis through the Jun **kinase** (JNK) pathway. The location of DAXX is of interest given the linkage of autoimmune disease to the MHC and to apoptosis.

L10 ANSWER 72 OF 93 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 1998078670 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9418861
TITLE: Myotonic dystrophy **kinase**-related Cdc42-binding **kinase** acts as a Cdc42 effector in promoting cytoskeletal reorganization.
AUTHOR: Leung T; Chen X Q; Tan I; Manser E; Lim L
CORPORATE SOURCE: Glaxo-IMCB Group, Institute of Molecular & Cell Biology, National University of Singapore, Kent Ridge, Singapore.
SOURCE: Molecular and cellular biology, (1998 Jan) 18 (1) 130-40. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF021935; GENBANK-AF021936
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980130
Last Updated on STN: 20020420
Entered Medline: 19980122

AB The Rho GTPases play distinctive roles in cytoskeletal reorganization associated with growth and differentiation. The Cdc42/Rac-binding p21-activated **kinase** (PAK) and Rho-binding **kinase** (ROK) act as morphological effectors for these GTPases. We have isolated two related novel brain **kinases** whose p21-binding domains resemble that of PAK whereas the **kinase** domains resemble that of myotonic dystrophy **kinase**-related ROK. These approximately 190-kDa myotonic dystrophy **kinase**-related Cdc42-binding **kinases** (MRCKs) preferentially phosphorylate nonmuscle **myosin light chain** at serine 19, which is known to be crucial for activating actin-myosin contractility. The p21-binding domain binds GTP-Cdc42 but not GDP-Cdc42. The multidomain structure includes a cysteine-rich motif resembling those of protein **kinase** C and n-chimaerin and a putative pleckstrin **homology** domain. MRCK alpha and Cdc42V12 colocalize, particularly at the cell periphery in transfected HeLa cells. Microinjection of plasmid encoding MRCK alpha resulted in actin and myosin reorganization. **Expression** of **kinase**-dead MRCK alpha blocked Cdc42V12-dependent formation of focal complexes and peripheral microspikes. This was not due to possible sequestration of the p21, as a **kinase**-dead MRCK alpha mutant defective in Cdc42 binding was an equally effective blocker. Coinjection of MRCK alpha plasmid with Cdc42 plasmid, at concentrations where Cdc42 plasmid by itself elicited no effect, led to the formation of the peripheral structures associated with a Cdc42-induced morphological phenotype. These Cdc42-type effects were not promoted upon coinjection with plasmids of **kinase**-dead or Cdc42-binding-deficient MRCK alpha mutants. These results suggest that MRCK alpha may act as a downstream effector of Cdc42 in cytoskeletal reorganization.

L10 ANSWER 73 OF 93 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 97304466 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9160829
TITLE: **Myosin light chain kinase** in endothelium: molecular **cloning** and regulation.
AUTHOR: Garcia J G; Lazar V; Gilbert-McClain L I; Gallagher P J; Verin A D
CORPORATE SOURCE: Department of Medicine, Indiana University School of Medicine, and Richard Roudebush Veterans Administration Center, Indianapolis, USA.
CONTRACT NUMBER: HL50533 (NHLBI)
HL57362 (NHLBI)
SOURCE: American journal of respiratory cell and molecular biology, (1997 May) 16 (5) 489-94.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U48959
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970617

AB The phosphorylation of **myosin light chains** by **myosin light chain kinase** (**MLCK**) is a key event in agonist-mediated endothelial cell gap formation and vascular permeability. We now report the **cloning** and **expression** of a nonmuscle **MLCK** isoform in cultured endothelium. Screening of a **human** endothelial cell cDNA library identified a 7.7 kb cDNA with substantial (> 95%) **homology** to the coding region of the rabbit and bovine smooth muscle (SM) **MLCK** (amino acid #923-1913) as well as with the reported avian nonmuscle **MLCK** (65-70% **homology**). Sequence analysis also identified, however, a 5' stretch of novel sequence (amino acids #1-922) which is not contained in the open reading frame of mammalian SM **MLCK**, and is only 58% **homologous** to the avian fibroblast **MLCK** sequence. Immunoprecipitation with NH2-specific antisera revealed a 214 kD high molecular weight **MLCK** in bovine and **human** endothelium which exhibits MLC phosphorylation properties. Amino acid sequence analysis revealed endothelial **MLCK** consensus sequences for a variety of protein **kinases** including highly conserved potential phosphorylation sites for cAMP-dependent protein **kinase** A (PKA) in the CaM-binding region. Augmentation of intracellular cAMP levels markedly enhanced **MLCK** phosphorylation (2.5-fold increase) and reduced **kinase** activity in **MLCK** immunoprecipitates (4-fold decrease). These data suggest potentially novel mechanisms of endothelial cell contraction and barrier regulation.

L10 ANSWER 74 OF 93 MEDLINE on STN
ACCESSION NUMBER: 97195483 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9042856
TITLE: Caenorhabditis elegans LET-502 is related to Rho-binding **kinases** and **human** myotonic dystrophy **kinase** and interacts genetically with a **homolog** of the regulatory subunit of smooth muscle myosin phosphatase to affect cell shape.
AUTHOR: Wissmann A; Ingles J; McGhee J D; Mains P E
CORPORATE SOURCE: University of Calgary, Department of Medical Biochemistry, Alberta, Canada.. wissmann@acs.ucalgary.ca
SOURCE: Genes & development, (1997 Feb 15) 11 (4) 409-22.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U14989; GENBANK-U85515; GENBANK-U86640; GENBANK-X71057; GENBANK-Z30329; GENBANK-Z30330
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970407
Last Updated on STN: 20020420
Entered Medline: 19970324

AB We have identified two genes associated with the hypodermal cell shape changes that occur during elongation of the Caenorhabditis elegans embryo. The first gene, called let-502, encodes a protein with high similarity to Rho-binding Ser/Thr **kinases** and to **human** myotonic dystrophy **kinase** (DM-**kinase**). Strong mutations in let-502 block embryonic elongation, and let-502 reporter constructs are **expressed** in hypodermal cells at the elongation stage of development. The second gene, mel-11, was identified by mutations that act as extragenic suppressors of let-502. mel-11 encodes a protein similar to the 110- to 133-kD regulatory subunits of vertebrate smooth muscle myosin-associated phosphatase (PP-1M). We suggest that the LET-502 **kinase** and the MEL-11 phosphatase subunit act in a pathway linking a signal generated by the small GTP-binding protein Rho to a myosin-based hypodermal contractile system that drives embryonic elongation. LET-502 may directly regulate the activity of the MEL-11 containing phosphatase complex and the similarity between LET-502 and DM-**kinase** suggests a similar function for DM-**kinase**.

L10 ANSWER 75 OF 93 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:851153 SCISEARCH
THE GENUINE ARTICLE: YF541
TITLE: Myosin phosphorylation by **human** cdc42-dependent S6/H4 **kinase**/gamma PAK from placenta and lymphoid cells
AUTHOR: Ramos E (Reprint); Wysolmerski R B; Masaracchia R A
CORPORATE SOURCE: UNIV N TEXAS, DEPT BIOL SCI, DIV BIOCHEM & MOL BIOL, DENTON, TX 76201; ST LOUIS UNIV, SCH MED, DEPT PATHOL & ANESTHESIOL, ST LOUIS, MO 63104
COUNTRY OF AUTHOR: USA
SOURCE: RECEPTORS & SIGNAL TRANSDUCTION, (DEC 1997) Vol. 7, No. 2, pp. 99-110.
Publisher: HUMANA PRESS INC, 999 RIVERVIEW DRIVE SUITE 208, TOTOWA, NJ 07512.
ISSN: 1052-8040.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 33
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The p21-activated **kinase** (PAK) family includes protein phosphotransferases regulated by the GTPases rho, rac, and cdc42. Sequence **homology**, activation mechanism, and substrate specificity suggest that the well-characterized **human** placenta S6/H4 **kinase** is a member of this family. In these studies, S6/H4 **kinase** purified to homogeneity from **human** placenta was activated in vitro by cdc42-GTP, or protease incubation and MgATP-dependent autophosphorylation. The cdc42-activated enzyme demonstrated an M-r 60,000, and shares sequence **homology** with the gamma PAK family. Antipeptide antibodies against one of the autophosphorylation site sequences recognized a single p60 protein in the purified placenta preparation or Jurkat cell extracts. An autophosphorylated M-r 40,000 protein, previously identified as the catalytic domain of the enzyme, was also detected by the antibody after protease activation. Crude PAK60 obtained from Mono Q chromatography of Jurkat cell extracts and purified placenta enzyme catalyzed phosphorylation of histone H4 and myelin basic protein as well as a variety of synthetic peptides previously identified

as S6/H4 **kinase** substrates. In addition, Jurkat myosin II and the regulatory **myosin light chain** were phosphorylated by the Jurkat and placenta gamma PAK. Synthetic peptides were used to demonstrate that the site of light chain phosphorylation occurs at the serine which results in ATPase activation. The data suggest that **human** gamma PAK may regulate cell motility by a GTP-dependent and calcium-independent mechanism.

L10 ANSWER 76 OF 93 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:509291 SCISEARCH
THE GENUINE ARTICLE: XH220
TITLE: Identification of MAPKAPK **homolog** (MAPKAPK-4) as a myosin II regulatory light-chain **kinase** in sea urchin egg extracts
AUTHOR: Komatsu S; Murai N; Totsukawa G; Abe M; Akasaka K; Shimada H; Hosoya H (Reprint)
CORPORATE SOURCE: HIROSHIMA UNIV, FAC SCI, DEPT BIOL SCI, HIGASHIHIROSHIMA 739, JAPAN (Reprint); HIROSHIMA UNIV, FAC SCI, DEPT BIOL SCI, HIGASHIHIROSHIMA 739, JAPAN; HIROSHIMA UNIV, MOL GENET LAB, GRAD DEPT GEN SCI, HIGASHIHIROSHIMA 739, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1 JUL 1997) Vol. 343, No. 1, pp. 55-62.
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0003-9861.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We identified and **cloned** a **homolog** of mammalian mitogen-activated protein **kinase**-activated protein **kinase** (MAPKAPK)-2 and -3 from sea urchin, Hemicentrotus pulcherrimus. The obtained cDNA **clone** was composed of 350 amino acid residues which contain MAPK phosphorylation sites and the bipartite nuclear localization signal sites in its C-terminal domain, The **clone** showed 65.4 and 66.7% amino acid residue identity to **human** MAPKAPK-2 and -3, respectively, Phylogenetic analysis revealed that the **homolog** can be classified into a distinct group of MAPKAPK and, therefore, the identified **homolog** was designated as MAPKAPK-4. Biochemical characterization was performed using **recombinant** glutathione S-transferase (GST)-MAPKAPK-4 fusion protein, The protein **kinase** activity of GST-MAPKAPK-4 was activated by MAPK and this enabled the **kinase** to phosphorylate both glycogen synthase N-terminal peptide and the regulatory light chain of myosin II in vitro, Northern blot analysis showed that MAPKAPK-4 was **expressed** throughout the development of sea urchin embryos, These observations suggest that MAPKAPK-4 may play an important role in the regulation of myosin II activity during the development of sea urchin. (C) 1997 Academic Press

L10 ANSWER 77 OF 93 MEDLINE on STN
ACCESSION NUMBER: 96224308 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8643598
TITLE: The multidomain protein Trio binds the LAR transmembrane tyrosine phosphatase, contains a protein **kinase** domain, and has separate rac-specific and rho-specific guanine nucleotide exchange factor domains.
AUTHOR: Debant A; Serra-Pages C; Seipel K; O'Brien S; Tang M; Park S H; Streuli M
CORPORATE SOURCE: Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston, MA 02115, USA.
CONTRACT NUMBER: CA 55547 (NCI)

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996 May 28) 93 (11) 5466-71. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U42390
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 20000303
Entered Medline: 19960717

AB rho-like GTP binding proteins play an essential role in regulating cell growth and actin polymerization. These molecular switches are positively regulated by guanine nucleotide exchange factors (GEFs) that promote the exchange of GDP for GTP. Using the interaction-trap assay to identify candidate proteins that bind the cytoplasmic region of the LAR transmembrane protein tyrosine phosphatase (PT-Pase), we isolated a cDNA encoding a 2861-amino acid protein termed Trio that contains three enzyme domains: two functional GEF domains and a protein serine/threonine **kinase** (PSK) domain. One of the Trio GEF domains (Trio GEF-D1) has rac-specific GEF activity, while the other Trio GEF domain (Trio GEF-D2) has rho-specific activity. The C-terminal PSK domain is adjacent to an Ig-like domain and is most similar to calcium/calmodulin-dependent **kinases**, such as smooth muscle **myosin light chain kinase** which similarly contains associated Ig-like domains. Near the N terminus, Trio has four spectrin-like repeats that may play a role in intracellular targeting. Northern blot analysis indicates that Trio has a broad tissue distribution. Trio appears to be phosphorylated only on serine residues, suggesting that Trio is not a LAR substrate, but rather that it forms a complex with LAR. As the LAR PTPase localizes to the ends of focal adhesions, we propose that LAR and the Trio GEF/PSK may orchestrate cell-matrix and cytoskeletal rearrangements necessary for cell migration.

L10 ANSWER 78 OF 93 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 96354791 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8753767
TITLE: Differential display and **cloning** of shear stress-responsive messenger RNAs in **human** endothelial cells.
AUTHOR: Ando J; Tsuboi H; Korenaga R; Takahashi K; Kosaki K; Isshiki M; Tojo T; Takada Y; Kamiya A
CORPORATE SOURCE: Department of Cardiovascular Biomechanics, Faculty of Medicine, University of Tokyo, Japan.
SOURCE: Biochemical and biophysical research communications, (1996 Aug 14) 225 (2) 347-51. Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19961022
Entered Medline: 19961010

AB To investigate the effect of shear stress on endothelial gene **expression**, we performed differential display of mRNAs from cultured **human** umbilical vein endothelial cells either incubated under static conditions or exposed to shear stress (15 dynes/cm2) for 6 h in a flow-chamber. Around 4% of the total number of mRNAs detected were either up- or down-regulated by shear stress. DNA sequencing of some of these shear stress-responsive mRNAs revealed **homology** of several **clones** to known gene sequences and many other **clones** for

unknown genes. Known genes, including those for **human** laminin B1 chain, H(+)-ATP synthase coupling factor 6, lysyl oxidase, **myosin light chain kinase**, and interleukin-8 receptor, were upregulated by shear stress, while the gene encoding NADH dehydrogenase was down-regulated. The present results suggest that shear stress can change the **expression** of numerous genes in endothelial cells, far more than reported to date, and that mRNA differential display is quite useful for **cloning** known and unknown shear stress-responsive genes.

L10 ANSWER 79 OF 93 MEDLINE on STN
ACCESSION NUMBER: 96409571 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8814553
TITLE: Primary structure of the **kinase** domain region of rabbit skeletal and cardiac muscle titin.
AUTHOR: Sebestyen M G; Fritz J D; Wolff J A; Greaser M L
CORPORATE SOURCE: Department of Meat and Animal Science, Waisman Center, University of Wisconsin-Madison 53705, USA.
CONTRACT NUMBER: HL47053 (NHLBI)
SOURCE: Journal of muscle research and cell motility, (1996 Jun) 17 (3) 343-8.
Journal code: 8006298. ISSN: 0142-4319.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U38275; GENBANK-X90568
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961122

AB A 2.3 kb region of rabbit cardiac and skeletal muscle titin has been **cloned**. The cDNA sequences of the two tissues are identical and show 91% identity on the nucleotide level with the corresponding region of **human** cardiac muscle titin. On the amino acid level the identity is 96% and similarity is 98%. Alignment of predicted amino acid sequences of several **homologous kinase** domains reveals that the rabbit titin **kinase** has all the necessary elements of an active catalytic domain and carries a potential regulatory region on its C-terminal end. The distance of the 2.3 kb contig from the 3' end of the message was determined to be 5.7 kb in both tissues using oligonucleotide directed RNase H cleavage of titin mRNAs. This is essentially identical with the length of the fully sequenced **human** cardiac titin C-terminal end. It therefore appears unlikely that there are major tissue specific differences in this 8 kb cDNA region which encodes the C-terminus of rabbit skeletal and cardiac titin.

L10 ANSWER 80 OF 93 MEDLINE on STN
ACCESSION NUMBER: 95331314 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7607248
TITLE: A calmodulin-binding sequence in the C-terminus of **human** cardiac titin **kinase**.
AUTHOR: Gautel M; Castiglione Morelli M A; Pfuhl M; Motta A; Pastore A
CORPORATE SOURCE: EMBL, Heidelberg, Germany.
SOURCE: European journal of biochemistry / FEBS, (1995 Jun 1) 230 (2) 752-9.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828

Last Updated on STN: 19950828
Entered Medline: 19950817

AB The giant muscle proteins of the titin family, which are specific for the striated muscles of vertebrates and invertebrates, contain as a common feature a catalytic protein **kinase** domain of so far unclear function and regulation. In **myosin light chain kinase**, a family evolutionarily related to titin, **kinase** regulation is achieved by calmodulin binding to a region of the **kinase** C-terminus which bears similarity to the substrate. A calmodulin-binding sequence has also been identified in the C-terminus of the Aplysia twitchin **kinase**. In analogy, we identified a putative calmodulin-binding site in the titin **kinase** C-terminal sequence. The **expressed** catalytic domain itself and a series of synthetic peptides from this region were tested for their ability to bind calmodulin. Biochemical data indicate that titin **kinase** as well as peptides from its C-terminus bind to calmodulin in an equimolar complex in the presence of calcium. The interaction of truncated peptides with calmodulin is, however, weaker than that of **myosin light chain kinase**. Nuclear magnetic resonance studies showed that these peptides have a tendency to adopt alpha-helical conformations in solution. Helicity increases upon binding of calmodulin in a calcium-dependent fashion, as judged by circular dichroism spectra. We, therefore, propose that this calmodulin-binding region of titin could play a regulatory role for the enzyme, the substrate of which still remains to be identified.

L10 ANSWER 81 OF 93 MEDLINE on STN
ACCESSION NUMBER: 96121365 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8575746
TITLE: The **human myosin light chain kinase** (**MLCK**) from hippocampus: **cloning**, sequencing, **expression**, and localization to 3qcen-q21.
AUTHOR: Potier M C; Chelot E; Pekarsky Y; Gardiner K; Rossier J; Turnell W G
CORPORATE SOURCE: Institut Alfred Fessard, Centre National de la Recherche Scientifique, Gif-sur-Yvette, France.
SOURCE: Genomics, (1995 Oct 10) 29 (3) 562-70.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X85337
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19960321
Entered Medline: 19960314

AB **Myosin light chain kinase** (**MLCK**), a key enzyme in muscle contraction, has been shown by immunohistology to be present in neurons and glia. We describe here the **cloning** of the cDNA for **human MLCK** from hippocampus, encoding a protein sequence 95% similar to smooth muscle **MLCKs** but less than 60% similar to skeletal muscle **MLCKs**. The cDNA **clone** detected two RNA transcripts in **human** frontal and entorhinal cortex, in hippocampus, and in jejunum, one corresponding to **MLCK** and the other probably to telokin, the carboxy-terminal 154 codons of **MLCK expressed** as an independent protein in smooth muscle. Levels of **expression** were lower in brain compared to smooth muscle. We show that within the protein sequence, a motif of 28 or 24 residues is repeated five times, the second repeat ending with the putative methionine start codon. These repeats overlap with a second previously reported module of 12 residues repeated five times in the **human** sequence. In addition, the acidic

C-terminus of all **MLCKs** from both brain and smooth muscle resembles the C-terminus of tubulins. The chromosomal localization of the gene for **human MLCK** is shown to be at 3qcen-q21, as determined by PCR and Southern blotting using two somatic cell hybrid panels.

L10 ANSWER 82 OF 93 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:475478 BIOSIS
DOCUMENT NUMBER: PREV199598489778
TITLE: Endothelial cells (EC) contain a **myosin light chain kinase** (**MLCK**): Partial **cloning** and characterization.
AUTHOR(S): Lazar, Virginie; Verin, Alexander D.; Patterson, Carolyn E.; Gallagher, Patricia J.; Garcia, Jose G. N.
CORPORATE SOURCE: Indiana Univ., Indianapolis, IN, USA
SOURCE: Journal of Investigative Medicine, (1995) Vol. 43, No. SUPPL. 3, pp. 441A.
Meeting Info.: Meeting of the Midwest Section of the American Federation for Clinical Research. Chicago, Illinois, USA. September 28-30, 1995.
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Nov 1995
Last Updated on STN: 1 Nov 1995

L10 ANSWER 83 OF 93 MEDLINE on STN
ACCESSION NUMBER: 94342273 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8063728
TITLE: Autophosphorylation of molluscan twitchin and interaction of its **kinase** domain with calcium/calmodulin.
AUTHOR: Heierhorst J; Probst W C; Vilim F S; Buku A; Weiss K R
CORPORATE SOURCE: Department of Physiology and Biophysics, Mount Sinai School of Medicine, New York, New York 10029.
CONTRACT NUMBER: GM32099 (NIGMS)
MH36730 (NIMH)
SOURCE: Journal of biological chemistry, (1994 Aug 19) 269 (33) 21086-93.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
OTHER SOURCE: GENBANK-Z30161
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19941005
Last Updated on STN: 19941005
Entered Medline: 19940921
AB An approximately 750-kDa member of the family of giant titin/twitchin-like myosin-associated proteins was highly purified from muscle of the marine mollusc Aplysia californica. Purified twitchin was able to autophosphorylate on threonine, which demonstrates its protein serine/threonine **kinase** activity. cDNA sequence analysis of the **cloned kinase** domain of molluscan twitchin revealed that it is most closely related with the **kinase** domains of Caenorhabditis elegans twitchin (62% identity) and vertebrate **myosin light chain kinases** (45% average identity). Analysis of the cDNA sequence further suggested the presence of a potential calmodulin-binding site in a putative autoinhibitory region. The functional activity of this site was demonstrated by the calcium-dependent binding of purified twitchin to

immobilized calmodulin and the fact that this interaction could be competed with synthetic peptides deduced from the cDNA sequence. Furthermore, biotinylated calmodulin bound to immobilized twitchin in gel-overlay assays with nanomolar affinity (EC50 approximately equal to 70 nM). The potential regulation of twitchin by calcium/calmodulin indicates that titin-like molecules may serve dynamic functions during contraction-relaxation cycles in muscle in addition to their functions as cytoskeletal proteins.

L10 ANSWER 84 OF 93 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:394964 BIOSIS
DOCUMENT NUMBER: PREV199396070264
TITLE: Rat ovarian 20-alpha-hydroxysteroid dehydrogenase 1 may belong to aldo-keto reductase superfamily.
AUTHOR(S): Noda, Ken; Yagi, Shintaro; Shiota, Kunio; Ogawa, Tomoya; Takahashi, Michio [Reprint author]
CORPORATE SOURCE: Vet. Pysiol. Vet. Med. Sci., Univ. Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan
SOURCE: Journal of Reproduction and Development, (1993) Vol. 39, No. 2, pp. 169-173.
ISSN: 0916-8818.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 1993
Last Updated on STN: 28 Sep 1993

AB We have previously purified the 20-alpha-hydroxysteroid dehydrogenase (20-alpha-HSD) molecule from normal mature rat ovarian cytosol (Biochim. Biophys. Acta, 1991, 1079: 112-118). In order to further characterize the 20-alpha-HSD and to obtain information for molecular **cloning** of the enzyme, we determined its N-terminal amino acid sequence. The sequence was shown to the Ser-Lys-Ile-Gln-Lys-Met-Glu-Leu-Asn-Asp-Gly-His-Ser-Ile-Pro-Val-Leu-Gly-Phe-Xaa-Thr. A search of the SWISS-PROT protein sequence database for N-terminal amino acid sequence similarities revealed 6 highly **homologous** proteins, including bovine prostaglandin F synthase, rat liver 3-alpha-hydroxysteroid dehydrogenase, bovine lens aldose reductase, **human** aldose reductase, frog epsilon-crystallin and **human** liver chlordecone reductase, suggesting that rat ovarian 20-alpha-HSD belongs to the aldo-keto reductase gene superfamily.

L10 ANSWER 85 OF 93 MEDLINE on STN
ACCESSION NUMBER: 94049975 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8232409
TITLE: Molecular **cloning** of a rac family protein **kinase** and identification of a serine/threonine protein **kinase** gene family of Entamoeba histolytica.
AUTHOR: Que X; Samuelson J; Reed S
CORPORATE SOURCE: Department of Pathology and Medicine, University of California, San Diego.
CONTRACT NUMBER: AI28035 (NIAID)
AI28395 (NIAID)
DK-35108 (NIDDK)
SOURCE: Molecular and biochemical parasitology, (1993 Aug) 60 (2) 161-70.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L06185; GENBANK-L06186; GENBANK-L06187; GENBANK-L06188; GENBANK-L06189; GENBANK-L06190; GENBANK-L06191; GENBANK-L06192; GENBANK-L06193; GENBANK-L06194; GENBANK-L06195; GENBANK-L06196

ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 20020420
Entered Medline: 19931126

AB Eleven Entamoeba histolytica protein-serine/threonine-**kinase** gene segments were identified using the polymerase chain reaction (PCR) and degenerate oligonucleotide primers to conserved amino acids in subdomains VI and VIII of the catalytic domain of protein-serine/threonine **kinases**. These ameba gene segments were **homologous** to **myosin light chain kinases**, protein **kinase** C, phosphorylase b **kinase**, and **kinases** that regulate glucose repression in yeast and cell growth in mammalian cells. One of these PCR products, which was **homologous** to the Dictyostelium discoideum protein **kinase** 2, was used to identify a full-length protein-serine/threonine-**kinase** gene (Eh rac1) from an E. histolytica genomic library. The open reading frame of Eh rac1 was 409 amino acids long (encoding a 47-kDa protein) and included an amino terminal segment containing 87 mostly charged and polar amino acids and a 322-amino acid carboxyl terminal segment containing the catalytic domain. The catalytic domain of Eh rac1 was **homologous** to the rac family of protein-serine/threonine-**kinases**, which are related to cAMP-dependent protein **kinases** and protein **kinase** Cs. Southern blots of ameba DNA showed that the Eh rac1 gene was present as a single copy in all strains tested, however pathogenic amebae **expressed** four times more Eh rac1 mRNAs than did nonpathogenic amebae. These studies suggest that E. histolytica, a primitive unicellular eukaryote, has a complex protein **kinase** family.

L10 ANSWER 86 OF 93 EMBASE
on STN
ACCESSION NUMBER: 92146849 EMBASE
DOCUMENT NUMBER: 1992146849
TITLE: Towards a molecular understanding of titin.
AUTHOR: Labeit S.; Gautel M.; Lakey A.; Trinick J.
CORPORATE SOURCE: European Molecular Biology Lab, Meyerhofstrasse 1,6900 Heidelberg, Germany
SOURCE: EMBO Journal, (1992) 11/5 (1711-1716).
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Titin is at present the largest known protein (M(r) 3000 kDa) and its **expression** is restricted to vertebrate striated muscle. Single molecules span from M- to Z-lines and therefore over 1 μm. We have isolated cDNAs encoding five distant titin A-band epitopes, extended their sequences and determined 30 kb (1000 kDa) of the primary structure of titin. Sequences near the M-line encode a **kinase** domain and are closely related to the C-terminus of twitchin from Caenorhabditis elegans. This suggests that the function of this region in the titin/twitchin family is conserved throughout the animal kingdom. All other A-band sequences consist of 100 amino acid (aa) repeats predicting immunoglobulin-C2 and fibronectin type m globular domains. These domains are arranged into highly ordered 11 domain super-repeat patterns likely to match the myosin helix repeat in the thick filament. **Expressed** titin fragments bind to the LMM part of myosin and C-protein. Binding strength increases with the number of domains involved, indicating a cumulative effect of multiple binding sites for myosin along the titin molecule. We conclude that A-band titin is likely to be involved in the the ordered assembly of the vertebrate thick filament.

L10 ANSWER 87 OF 93 MEDLINE on STN
ACCESSION NUMBER: 93081726 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1450380
TITLE: Novel protein **kinase** of Arabidopsis thaliana (APK1) that phosphorylates tyrosine, serine and threonine.
AUTHOR: Hirayama T; Oka A
CORPORATE SOURCE: Laboratory of Molecular Genetics, Institute for Chemical Research, Kyoto University, Japan.
SOURCE: Plant molecular biology, (1992 Nov) 20 (4) 653-62.
Journal code: 9106343. ISSN: 0167-4412.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-D01186; GENBANK-D10152
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930129
Last Updated on STN: 19930129
Entered Medline: 19930107

AB During the course of characterizing polymerase chain reaction products corresponding to protein **kinases** of a higher plant, Arabidopsis thaliana, we found a DNA fragment that potentially codes for a polypeptide with mosaic sequences of two classes of protein **kinases**, a tyrosine-specific and a serine/threonine-specific one. Overlapping complementary DNA (cDNA) **clones** coinciding with this fragment were isolated from an A. thaliana cDNA library. From their sequence analyses a protein **kinase** was predicted composed of 410 amino acid residues (APK1, Arabidopsis protein **kinase** 1), in which the **kinase** domain was flanked by short non-**kinase** domains.
Upon **expression** of APK1 in Escherichia coli cells, several bacterial proteins became reactive with anti-phosphotyrosine antibody but not with the same antibody preincubated with phosphotyrosine, convincing us that APK1 phosphorylated tyrosine residues. APK1 purified from an over-producing E. coli strain showed serine/threonine **kinase** activity, and no tyrosine **kinase** activity, towards APK1 itself, casein, enolase, and **myosin light chains**.
APK1 was thus concluded to be a novel type of protein **kinase**, which could phosphorylate tyrosine, serine, and threonine residues, though tyrosine phosphorylation seemed to occur only on limited substrates. Since the structure of the APK1 N-terminal portion was indicative of N-myristoylation, APK1 might associate with membranes and thereby contribute to signal transduction. The A. thaliana genome contained two APK1 genes close to each other (APK1a and APK1b).

L10 ANSWER 88 OF 93 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 94069407 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1341033
TITLE: cDNA **cloning** and sequence comparisons of **human** and chicken muscle C-protein and 86kD protein.
AUTHOR: Vaughan K T; Weber F E; Fischman D A
CORPORATE SOURCE: Department of Cell Biology and Anatomy, Cornell University Medical College, New York, NY 10021.
CONTRACT NUMBER: AR32147 (NIAMS)
SOURCE: Symposia of the Society for Experimental Biology, (1992) 46 167-77.
Journal code: 0404517. ISSN: 0081-1386.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19940201
Entered Medline: 19931227

AB Thick filaments in vertebrate striated muscles are composed of myosin

heavy chain (MHC) and **myosin light chains** (MLCs) plus at least eight other proteins: C-protein, 86kD protein (birds) or H-protein (mammals), M-protein, myomesin, titin, MM-creatine **kinase**, skelemin, and AMP-deaminase. Except for CPK and AMP deaminase, none have well defined functions. Analysis of cDNA **clones** encoding chicken C-protein and 86kD protein has revealed a high degree of shared amino acid identity, particularly in the C-terminal 40kD. To identify functionally significant regions, the **human** counterpart of each protein was **cloned**, sequenced and analysed. Two **human** C-protein cDNAs were isolated with significant **homology** to chicken fast C-protein. **Clone** H75, with 69% identity to chicken fast C-protein, shows the same pattern of hybridization as the chicken fast C-protein in chicken muscles. The other **clone**, H8 with 60% identity, shows a pattern of hybridization in chicken muscles which is consistent with the **expression** of chicken slow C-protein. The **human** 86kD protein shares 66% DNA sequence identity with the chicken 86kD protein. Assuming that essential sequences would be conserved during evolution, we compared the chicken and **human** proteins using PALIGN. Chicken and **human** fast C-proteins possess 66% peptide identity over their deduced length plus 10% conservative substitutions. **Human** slow C-protein and chicken fast C-protein share 44% peptide sequence identity, plus 16% conservative substitutions. Chicken and **human** 86kD proteins are also very similar: 54% peptide identity plus 20% conservative substitutions. This high degree of sequence identity between chicken and **human** C- and 86kD proteins suggests selective pressure on the primary sequence. Recent primary sequence analyses of projectin and mini-titins from Drosophila, twitchin from C. elegans, C-protein, smMLCK, 86kD protein, and M-protein from the chicken, titin from the rabbit, and skelemin from the mouse reveals that all these proteins possess multiple internal repeats of approximately 100 amino acids. These repeating domains are of two types: one is **homologous** to the internal repeats which define the C-2 subset of the immunoglobulin superfamily, the other is related to the fibronectin type III repeat. Both **human** C-proteins possess comparable internal repeats and preliminary evidence suggests the presence of the same repeats in **human** 86kD. This duality of repeat structure is found in many extracellular proteins and is typified by the N-CAMs.(ABSTRACT TRUNCATED AT 400 WORDS)

L10 ANSWER 89 OF 93 MEDLINE on STN
ACCESSION NUMBER: 92084694 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1748666
TITLE: Molecular characterization of a mammalian smooth muscle **myosin light chain kinase.**
COMMENT: Erratum in: J Biol Chemical 1992 May 5;267(13):9450. PubMed ID: 1577772
AUTHOR: Gallagher P J; Herring B P; Griffin S A; Stull J T
CORPORATE SOURCE: Department of Physiology, University of Texas Southwestern Medical Center, Dallas 75235-9040.
CONTRACT NUMBER: 2 SO7 RR 07175 (NCRR)
HL26043 (NHLBI)
SOURCE: Journal of biological chemistry, (1991 Dec 15) 266 (35) 23936-44.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M55199; GENBANK-M55200; GENBANK-M55201; GENBANK-M76233; GENBANK-M76369; GENBANK-M96682; GENBANK-S66610; GENBANK-S66768; GENBANK-S70234; GENBANK-S70236
ENTRY MONTH: 199201

ENTRY DATE: Entered STN: 19920209
Last Updated on STN: 19920209
Entered Medline: 19920117

AB A 5.6-kilobase cDNA **clone** has been isolated which includes the entire coding region for the **myosin light chain kinase** from rabbit uterine tissue. This cDNA, **expressed** in COS cells, encodes a Ca2+/calmodulin-dependent protein **kinase** with catalytic properties similar to other purified smooth muscle **myosin light chain kinases**. A module (TLKPVGNIKPAE), repeated sequentially 15 times, has been identified near the N terminus of this smooth muscle **kinase**. It is not present in chicken gizzard or rabbit skeletal muscle **myosin light chain kinases**. This repeat module and a subrepeat (K P A/V) are similar in amino acid content to repeated motifs present in other proteins, some of which have been shown to associate with chromatin structures. Immunoblot analysis after sodium dodecyl sulfate-polyacrylamide gel electrophoresis, used to compare **myosin light chain kinase** present in rabbit, bovine, and chicken smooth and nonmuscle tissues, showed that within each species both tissue types have **myosin light chain kinases** with indistinguishable molecular masses. These data suggest that **myosin light chain kinases** present in smooth and nonmuscle tissues are the same protein.

L10 ANSWER 90 OF 93 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:546563 SCISEARCH
THE GENUINE ARTICLE: GH250
TITLE: MUSCLE-SPECIFIC GENE-**EXPRESSION** IN RHABDOMYOSARCOMAS AND STAGES OF **HUMAN** FETAL SKELETAL-MUSCLE DEVELOPMENT
AUTHOR: TONIN P N; SCRABLE H; SHIMADA H; CAVENEE W K (Reprint)
CORPORATE SOURCE: LUDWIG INST CANC RES, MONTREAL BRANCH, 687 PINE AVE W, MONTREAL H3A 1A1, QUEBEC, CANADA; CHILDRENS HOSP LOS ANGELES, DEPT PATHOL, LOS ANGELES, CA, 90027; MCGILL UNIV, DEPT MED, MONTREAL H3A 2B4, QUEBEC, CANADA; MCGILL UNIV, DEPT PATHOL, MONTREAL H3A 2B4, QUEBEC, CANADA; MCGILL UNIV, DEPT BIOL, MONTREAL H3A 2B4, QUEBEC, CANADA; MCGILL UNIV, DEPT NEUROL, MONTREAL H3A 2B4, QUEBEC, CANADA
COUNTRY OF AUTHOR: CANADA; USA
SOURCE: CANCER RESEARCH, (1991) Vol. 51, No. 19, pp. 5100-5106.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 57
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Rhabdomyosarcomas (RMS) bear a morphological resemblance to developing striated muscle. It has been reported that two histologically distinct subtypes of RMS, embryonal and alveolar, behave differently in many clinical aspects, such as age distribution, primary site, and prognosis. We have investigated the **expression** of various genes, which are preferentially **expressed** in normal muscle tissue or cell culture myosins, and creatine **kinases**, and myogenic regulatory genes MyoD, myogenin, MRF4, and Myf5), in embryonal and alveolar subtypes and compared the results to the stages of developing **human** fetal limb muscle. The data showed that each of the RMS tumors tested, regardless of histological features, **expressed** MyoD1 and MRF4 transcripts. **Expression** of the myogenin gene was detectable in all alveolar RMS (n = 8), whereas only 5 of 8 embryonal RMS **expressed** myogenin transcripts. Trace levels of Myf5 transcripts were visible in all alveolar RMS and 7 of 8 embryonal RMS. The alpha-skeletal, alpha-cardiac, and beta- and gamma-cytoplasmic actin transcripts were detectable in all alveolar RMS. While the beta- and gamma-cytoplasmic actin transcripts were evident in all embryonal RMS,

only 3 of 8 and 6 of 8 embryonal RMS **expressed** detectable levels of alpha-skeletal and alpha-cardiac actin transcripts, respectively. The embryonic form of myosin heavy chain was detectable in 1 of 8 of each type of tumor. **Myosin light chain**-1/3 transcripts were detectable in 4 of 8 alveolar RMS and 5 of 8 embryonal RMS. Brain creatine **kinase** transcripts were detectable in all alveolar RMS and 4 of 8 embryonal RMS, whereas none of the RMS samples contained detectable levels of the muscle form of creatine **kinase** . A comparison of the **expression** profiles with those of normal developing **human** fetal limb muscle (from 7.5 to 24 weeks' gestation) suggested that RMS resembled a relatively restricted segment of fetal muscle development. Furthermore, the data also showed a great deal of overlap in the differentiation state achieved by the embryonal and alveolar subtypes of RMS, suggesting that the clinicopathological difference between these two may not be due to malignant transformation of the cells from different positions in the normal pathway of myogenesis.

L10 ANSWER 91 OF 93 MEDLINE on STN
ACCESSION NUMBER: 90192766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2315308
TITLE: Isolation and characterization of a cDNA **clone** encoding avian skeletal muscle C-protein: an intracellular member of the immunoglobulin superfamily.
AUTHOR: Einheber S; Fischman D A
CORPORATE SOURCE: Department of Cell Biology and Anatomy, Cornell University Medical College, New York, NY 10021.
CONTRACT NUMBER: AR32147 (NIAMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1990 Mar) 87 (6) 2157-61. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M31209
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19970203
Entered Medline: 19900425

AB C-protein is a thick filament-associated protein located in the crossbridge region of vertebrate striated muscle A bands. Its function is unknown. To improve our understanding of its primary structure, we undertook the molecular **cloning** of C-protein mRNA. We describe the isolation and characterization of a cDNA **clone**, lambda C-86, that encodes approximately 80% of the fast isoform of C-protein in the chicken. Sequence analysis of the insert revealed that C-protein, although an intracellular, nonmembrane-associated protein, is a member of the immunoglobulin superfamily. Like several cell surface adhesion molecules that belong to this superfamily, C-protein contains sequence motifs that resemble immunoglobulin domains and fibronectin type III repeats. Computer searches using the C-protein sequence also lead to the identification of related domains in chicken smooth muscle **myosin light chain kinase** that have not been reported previously.

L10 ANSWER 92 OF 93 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 90097919 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2601707
TITLE: A new myocyte-specific enhancer-binding factor that recognizes a conserved element associated with multiple muscle-specific genes.
AUTHOR: Gossett L A; Kelvin D J; Sternberg E A; Olson E N
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Texas, M.D. Anderson Cancer Center, Houston

77030.
CONTRACT NUMBER: AR 39849 (NIAMS)
CA-16672 (NCI)
SOURCE: Molecular and cellular biology, (1989 Nov) 9 (11) 5022-33.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19900202

AB Exposure of skeletal myoblasts to growth factor-deficient medium results in transcriptional activation of muscle-specific genes, including the muscle creatine **kinase** gene (mck). Tissue specificity, developmental regulation, and high-level **expression** of mck are conferred primarily by a muscle-specific enhancer located between base pairs (bp) -1350 and -1048 relative to the transcription initiation site (E. A. Sternberg, G. Spizz, W. M. Perry, D. Vizard, T. Weil, and E. N. Olson, Mol. Cell. Biol. 8:2896-2909, 1988). To begin to define the regulatory mechanisms that mediate the selective activation of the mck enhancer in differentiating muscle cells, we have further delimited the boundaries of this enhancer and analyzed its interactions with nuclear factors from a variety of myogenic and nonmyogenic cell types. Deletion mutagenesis showed that the region between 1,204 and 1,095 bp upstream of mck functions as a weak muscle-specific enhancer that is dependent on an adjacent enhancer element for strong activity. This adjacent activating element does not exhibit enhancer activity in single copy but acts as a strong enhancer when multimerized. Gel retardation assays combined with DNase I footprinting and diethyl pyrocarbonate interference showed that a nuclear factor from differentiated C2 myotubes and BC3H1 myocytes recognized a conserved A + T-rich sequence within the peripheral activating region. This myocyte-specific enhancer-binding factor, designated MEF-2, was undetectable in nuclear extracts from C2 or BC3H1 myoblasts or several nonmyogenic cell lines. MEF-2 was first detectable within 2 h after exposure of myoblasts to mitogen-deficient medium and increased in abundance for 24 to 48 h thereafter. The appearance of MEF-2 required ongoing protein synthesis and was prevented by fibroblast growth factor and type beta transforming growth factor, which block the induction of muscle-specific genes. A myoblast-specific factor that is down regulated within 4 h after removal of growth factors was also found to bind to the MEF-2 recognition site. A 10-bp sequence, which was shown by DNase I footprinting and diethyl pyrocarbonate interference to interact directly with MEF-2, was identified within the rat and **human** mck enhancers, the rat **myosin light-chain** (mlc)-1/3 enhancer, and the chicken cardiac mlc-2A promoter. Oligomers corresponding to the region of the mlc-1/3 enhancer, which encompasses this conserved sequence, bound MEF-2 and competed for its binding to the mck enhancer. These results thus provide evidence for a novel myocyte-specific enhancer-binding factor, MEF-2, that is **expressed** early in the differentiation program and is suppressed by specific polypeptide growth factors. The ability of MEF-2 to recognize conserved activating elements associated with multiple-specific genes suggests that this factor may participate in the coordinate regulation of genes during myogenesis.

L10 ANSWER 93 OF 93 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 89323116 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2526655
TITLE: Characterization and differential **expression** of **human** vascular smooth muscle **myosin light chain** 2 isoform in nonmuscle cells.
AUTHOR: Kumar C C; Mohan S R; Zavodny P J; Narula S K; Leibowitz P

J
CORPORATE SOURCE: Department of Tumor Biology, Schering Corporation, Bloomfield, New Jersey 07003.
SOURCE: Biochemistry, (1989 May 2) 28 (9) 4027-35. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-J02854
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19890829

AB The 20-kDa regulatory **myosin light chain** (MLC), also known as MLC-2, plays an important role in the regulation of both smooth muscle and nonmuscle cell contractile activity. Phosphorylation of MLC-2 by the enzyme MLC **kinase** increases the actin-activated myosin ATPase activity and thereby regulates the contractile activity. We have isolated and characterized an MLC-2 cDNA corresponding to the **human** vascular smooth muscle MLC-2 isoform from a cDNA library derived from umbilical artery RNA. The translation of the in vitro synthesized mRNA, corresponding to the cDNA insert, in a rabbit reticulocyte lysate results in the synthesis of a 20,000-dalton protein that is immunoreactive with antibodies raised against purified chicken gizzard MLC-2. The derived amino acid sequence of the putative **human** smooth muscle MLC-2 shows only three amino acid differences when compared to chicken gizzard MLC-2. However, comparison with the **human** cardiac isoform reveals only 48% **homology**. Blot hybridizations and S1 nuclease analysis indicate that the **human** smooth muscle MLC-2 isoform is **expressed** restrictively in smooth muscle tissues such as colon and uterus and in some, but not all, nonmuscle cell lines. Previously reported MLC-2 cDNA from rat aortic smooth muscle cells in culture is ubiquitously **expressed** in all muscle and nonmuscle cells, and it was suggested that both smooth muscle and nonmuscle MLC-2 proteins are identical and are probably encoded by the same gene. In contrast, the **human** smooth muscle MLC-2 cDNA that we have characterized from an intact smooth muscle tissue is not **expressed** in skeletal and cardiac muscles and also in a number of nonmuscle cells.(ABSTRACT TRUNCATED AT 250 WORDS)

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=> s "valine 68" or "val 68" or "v68"
L11         129 "VALINE 68" OR "VAL 68" OR "V68"

=> s "alanine 68" or "ala 68" or "A68"
L12         609 "ALANINE 68" OR "ALA 68" OR "A68"

=> s "serine 545" or "ser 545" or "S545"
L13          20 "SERINE 545" OR "SER 545" OR "S545"

=> s "alanine 869" or "ala 869" or "A869"
L14           5 "ALANINE 869" OR "ALA 869" OR "A869"

=> s l11 or l12 or l13 or l14
L15         764 L11 OR L12 OR L13 OR L14

=> d his

     (FILE 'HOME' ENTERED AT 15:24:46 ON 03 MAY 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:25:12 ON 03 MAY 2004
L1       1194984 S KINASE?
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L2         26686 S "MYOSIN LIGHT CHAIN"
L3          3175 S "MLCK"
L4         27074 S L2 OR L3
L5          1266 S L4 AND (HOMOLOG? OR SUBFAMIL?)
L6           654 S L1 AND L5
L7       6504283 S CLON? OR EXPRESS? OR RECOMBINANT
L8           337 S L6 AND L7
L9           146 S HUMAN AND L8
L10           93 DUP REM L9 (53 DUPLICATES REMOVED)
L11          129 S "VALINE 68" OR "VAL 68" OR "V68"
L12          609 S "ALANINE 68" OR "ALA 68" OR "A68"
L13           20 S "SERINE 545" OR "SER 545" OR "S545"
L14            5 S "ALANINE 869" OR "ALA 869" OR "A869"
L15          764 S L11 OR L12 OR L13 OR L14

=> e wei m h/au
E1             8     WEI M F/AU
E2             5     WEI M G/AU
E3           133 --> WEI M H/AU
E4             1     WEI M H Y/AU
E5             1     WEI M I/AU
E6            41     WEI M J/AU
E7             6     WEI M K/AU
E8           102     WEI M L/AU
E9            20     WEI M M/AU
E10            1     WEI M N/AU
E11          106     WEI M Q/AU
E12            1     WEI M R/AU

=> s e3-e4
L16          134 ("WEI M H"/AU OR "WEI M H Y"/AU)

=> e difrancesco v/au
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E2             1     DIFRANCESCO U M/AU
E3            96 --> DIFRANCESCO V/AU
E4            15     DIFRANCESCO VALENTINA/AU
E5             1     DIFRANCESCOL/AU
E6             1     DIFRANCESO D/AU
E7             2     DIFRANCESO L/AU
E8             1     DIFRANCESO R/AU
E9             1     DIFRANCESO ROBIN/AU
E10            1     DIFRANCESSO L/AU
E11            6     DIFRANCIA C/AU
E12            4     DIFRANCIA CELENE/AU

=> s e3-e4
L17          111 ("DIFRANCESCO V"/AU OR "DIFRANCESCO VALENTINA"/AU)

=> e beasley e m/au
E1             1     BEASLEY E H/AU
E2             6     BEASLEY E L/AU
E3           291 --> BEASLEY E M/AU
E4             7     BEASLEY E O/AU
E5             1     BEASLEY E S G/AU
E6             2     BEASLEY E T/AU
E7             4     BEASLEY E W/AU
E8             2     BEASLEY E W 3RD/AU
E9             2     BEASLEY E W III/AU
E10            1     BEASLEY E W JR/AU
E11            1     BEASLEY EDWARD E/AU
E12            1     BEASLEY EDWARD EVANS/AU

=> s e3
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L18         291 "BEASLEY E M"/AU

=> d his

     (FILE 'HOME' ENTERED AT 15:24:46 ON 03 MAY 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:25:12 ON 03 MAY 2004
L1       1194984 S KINASE?
L2         26686 S "MYOSIN LIGHT CHAIN"
L3          3175 S "MLCK"
L4         27074 S L2 OR L3
L5          1266 S L4 AND (HOMOLOG? OR SUBFAMIL?)
L6           654 S L1 AND L5
L7       6504283 S CLON? OR EXPRESS? OR RECOMBINANT
L8           337 S L6 AND L7
L9           146 S HUMAN AND L8
L10           93 DUP REM L9 (53 DUPLICATES REMOVED)
L11          129 S "VALINE 68" OR "VAL 68" OR "V68"
L12          609 S "ALANINE 68" OR "ALA 68" OR "A68"
L13           20 S "SERINE 545" OR "SER 545" OR "S545"
L14            5 S "ALANINE 869" OR "ALA 869" OR "A869"
L15          764 S L11 OR L12 OR L13 OR L14
                 E WEI M H/AU
L16          134 S E3-E4
                 E DIFRANCESCO V/AU
L17          111 S E3-E4
                 E BEASLEY E M/AU
L18          291 S E3

=> s l15 or l16 or l17 or l18
L19         1279 L15 OR L16 OR L17 OR L18

=> s l9 and l19
L20            1 L9 AND L19

=> d all

L20   ANSWER 1 OF 1  BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN    2002-18305  BIOTECHDS
TI    New kinase proteins related to myosin light
      chain kinase subfamily and encoding
      polynucleotide, useful for diagnosing, treating disease or condition
      mediated by the kinase protein and for identifying modulators;
         vector-mediated recombinant protein gene transfer and
         expression in host cell, DNA chip and DNA microarray for use
         in drug screening, disease diagnosis, therapy, gene therapy and
         pharmacogenomics
AU    WEI M; KETCHUM K; DI FRANCESCO V; BEASLEY E M
PA    PE CORP NY
PI    WO 2002040683 23 May 2002
AI    WO 2000-US32616 14 Nov 2000
PRAI  US 2001-858664 17 May 2001
DT    Patent
LA    English
OS    WPI: 2002-500223 [53]
AB    DERWENT ABSTRACT:
      NOVELTY - An isolated human kinase peptide (I)
      consisting of or comprising a sequence (S1) of 1665 amino acids, an
      allelic variant or ortholog of (S1) encoded by a nucleic acid molecule
      (II) that hybridizes under stringent conditions to the opposite strand of
      a nucleic acid molecule having a sequence (S2) of 5207 base pairs as
      given in specification or fragment of (S1) having 10 contiguous amino
      acids, is new.
```

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (II) consisting of or comprising a nucleotide sequence (or its complement) that encodes (I), its allelic variant, ortholog or fragment; (2) an isolated antibody (III) that selectively binds to (I); (3) a gene chip comprising (II); (4) a transgenic non-**human** animal comprising (II); (5) a nucleic acid vector (IV) comprising (II); (6) a host cell (V) containing (IV); (7) producing (I); (8) detecting the presence of (I) in a sample, by contacting the sample with a detection agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide; (9) detecting the presence of (II) in a sample by contacting the sample with an oligonucleotide that hybridizes to the nucleic acid molecule under stringent conditions and determining whether the oligonucleotide binds to the nucleic acid molecule in the sample; (10) identifying a modulator of (I) comprising contacting (a cell **expressing**) (I) with an agent and determining if the agent has modulated the function or activity of (I); (11) identifying an agent that binds to (I) comprising contacting (I) with an agent and assaying the mixture to determine whether a complex is formed with the agent bound to (I); (12) a pharmaceutical composition (PC) comprising an agent identified using (I); (13) an isolated **human kinase** peptide (VI) having an amino acid sequence that shares at least 70% **homology** with (S1); and (12) an isolated nucleic acid molecule encoding a **human kinase** peptide, sharing at least 80% **homology** with (S2).

WIDER DISCLOSURE - Also disclosed are: (1) new agents identified by screening assays using (I); (2) kits comprising (III), to detect the presence of a protein in a sample; (3) kits for detecting the presence of a **kinase** nucleic acid in a biological sample; and (4) nucleic acid detection kit, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information of (II).

BIOTECHNOLOGY - Preparation: (I) is prepared by introducing (II) into a host cell, and culturing the host cell under conditions in which the peptides are **expressed** from the nucleotide sequence (claimed). Preferred Peptide: (VI) shares at lest 90% **homology** with (S1). Preferred Method: In the method for identifying a modulator of (I), the agent is administered to a host cell comprising an **expression** vector that **expresses** (I).

ACTIVITY - None given.

MECHANISM OF ACTION - Gene therapy. No supporting data is given.

USE - An agent identified using (I) is useful for treating a disease or condition mediated by a **human kinase** protein (claimed). (I) and (II) are useful as models for the development of **human** therapeutic targets, aid in the identification of therapeutic proteins and serve as targets for the development of **human** therapeutic agents that modulate **kinase** activity in cells and tissues that **express** the **kinase**. (I) and (II) are further useful as a query sequence to perform a search against sequence databases to identify other family members or related sequences. (I) is useful to raise antibodies or elicit another immune response, as a reagent in assays designed to quantitatively determine levels of the protein in biological fluids, and as markers for tissues in which the corresponding protein is **expressed** and to identify the binding partner/ligand so as to develop a system to identify inhibitors of the binding interactions. (I) is useful in competition binding assays to discover compounds that interact with the **kinase**. The **kinase**-modulating agents are useful in an animal or other model to determine the efficacy, toxicity, mechanism of action or side effects of treatment with such an agent. The **kinase** proteins also provide a target for diagnosing a disease or predisposition to a disease mediated by the peptide, in pharmacogenomic analysis and for treating disorders characterized by an absence of inappropriate, or unwanted **expression** of the protein. (II) is useful as primers for polymerase chain reaction (PCR) to amplify any given region of a nucleic

acid molecule and to synthesize antisense molecules of desired length and sequences, for constructing **recombinant** vectors, **expressing** antigenic portions of the proteins, as probes for determining the chromosomal positions of the nucleic acid molecules by in situ hybridization, making vectors containing the gene regulatory regions of the nucleic acid molecules, designing ribozymes, constructing host cells **expressing** a part, or all of (II), constructing transgenic animals, as hybridization probes for determining the presence, level, form and distribution of nucleic acid **expression**, to detect the presence of, or to determine levels of a specific nucleic acid molecule in cells, tissues, and in organisms and for drug screening to identify compounds that modulate **kinase** nucleic acid **expression**. (II) is further useful for monitoring the effectiveness of modulating compounds on the **expression** or activity of the **kinase** gene in clinical trials or in a treatment regimen, in diagnostic assays for qualitative change in **kinase** nucleic acid **expression** and for testing an individual for a genotype. (III) is useful to isolate, purify and detect the presence of (I) in cells or tissues to determine the pattern of **expression** of the protein among various tissues in an organism, to assess abnormal tissue distribution or abnormal **expression** during development or progression of a biological condition, to assess normal and aberrant subcellular localization of cells in various tissues in an organism, in pharmacogenomic analysis, for tissue typing and for inhibiting protein function. (V) is useful for producing a **kinase** protein or peptide, conducting cell-based assays involving the **kinase** protein, identifying **kinase** protein mutants and to produce non-**human** transgenic animals which are useful for studying the function of a **kinase** protein and identifying and evaluating modulators of **kinase** protein activity. (96 pages)

CC THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Genomic Technologies; GENETIC TECHNIQUES and APPLICATIONS, Transgenic Animals and Animal Models; BIOINFORMATICS and ANALYSIS, Biochips and Bioarrays; DIAGNOSTICS, Molecular Diagnostics; THERAPEUTICS, Gene Therapy

CT **HUMAN RECOMBINANT MYOSIN LIGHT CHAIN** PROTEIN-**KINASE** PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, **EXPRESSION** IN HOST CELL, DNA CHIP, DNA MICROARRAY, ANTIBODY, TRANSGENIC ANIMAL MODEL CONSTRUCTION, DNA PRIMER, DNA PROBE, RIBOZYME, APPL. DRUG SCREENING, DISEASE DIAGNOSIS, THERAPY, GENE THERAPY, PHARMACOGENOMICS ENZYME EC-2.7.1.37 BIOCHIP DNA ARRAY DNA AMPLIFICATION HYBRIDIZATION RNA ENZYME DNA SEQUENCE PROTEIN SEQUENCE (21, 49)

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(FILE 'HOME' ENTERED AT 15:24:46 ON 03 MAY 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 15:25:12 ON 03 MAY 2004

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L1      1194984 S KINASE?
L2        26686 S "MYOSIN LIGHT CHAIN"
L3         3175 S "MLCK"
L4        27074 S L2 OR L3
L5         1266 S L4 AND (HOMOLOG? OR SUBFAMIL?)
L6          654 S L1 AND L5
L7      6504283 S CLON? OR EXPRESS? OR RECOMBINANT
L8          337 S L6 AND L7
L9          146 S HUMAN AND L8
L10          93 DUP REM L9 (53 DUPLICATES REMOVED)
L11         129 S "VALINE 68" OR "VAL 68" OR "V68"
L12         609 S "ALANINE 68" OR "ALA 68" OR "A68"
L13          20 S "SERINE 545" OR "SER 545" OR "S545"
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L14             5 S "ALANINE 869" OR "ALA 869" OR "A869"
L15           764 S L11 OR L12 OR L13 OR L14
                  E WEI M H/AU
L16           134 S E3-E4
                  E DIFRANCESCO V/AU
L17           111 S E3-E4
                  E BEASLEY E M/AU
L18           291 S E3
L19          1279 S L15 OR L16 OR L17 OR L18
L20             1 S L9 AND L19

=> s l15 and l19
L21           764 L15 AND L19

=> s l6 and l19
L22             1 L6 AND L19

=> d ibib ab

L22   ANSWER 1 OF 1  BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-18305  BIOTECHDS
TITLE:            New kinase proteins related to myosin
                  light chain kinase
                  subfamily and encoding polynucleotide, useful for
                  diagnosing, treating disease or condition mediated by the
                  kinase protein and for identifying modulators;
                     vector-mediated recombinant protein gene transfer and
                     expression in host cell, DNA chip and DNA microarray for
                     use in drug screening, disease diagnosis, therapy, gene
                     therapy and pharmacogenomics
AUTHOR:           WEI M; KETCHUM K; DI FRANCESCO V; BEASLEY E M
PATENT ASSIGNEE:  PE CORP NY
PATENT INFO:      WO 2002040683 23 May 2002
APPLICATION INFO: WO 2000-US32616 14 Nov 2000
PRIORITY INFO:    US 2001-858664 17 May 2001
DOCUMENT TYPE:    Patent
LANGUAGE:         English
OTHER SOURCE:     WPI: 2002-500223 [53]
AB    DERWENT ABSTRACT:
      NOVELTY - An isolated human kinase peptide (I) consisting of or
      comprising a sequence (S1) of 1665 amino acids, an allelic variant or
      ortholog of (S1) encoded by a nucleic acid molecule (II) that hybridizes
      under stringent conditions to the opposite strand of a nucleic acid
      molecule having a sequence (S2) of 5207 base pairs as given in
      specification or fragment of (S1) having 10 contiguous amino acids, is
      new.
           DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the
      following: (1) an isolated nucleic acid molecule (II) consisting of or
      comprising a nucleotide sequence (or its complement) that encodes (I),
      its allelic variant, ortholog or fragment; (2) an isolated antibody (III)
      that selectively binds to (I); (3) a gene chip comprising (II); (4) a
      transgenic non-human animal comprising (II); (5) a nucleic acid vector
      (IV) comprising (II); (6) a host cell (V) containing (IV); (7) producing
      (I); (8) detecting the presence of (I) in a sample, by contacting the
      sample with a detection agent that specifically allows detection of the
      presence of the peptide in the sample and then detecting the presence of
      the peptide; (9) detecting the presence of (II) in a sample by contacting
      the sample with an oligonucleotide that hybridizes to the nucleic acid
      molecule under stringent conditions and determining whether the
      oligonucleotide binds to the nucleic acid molecule in the sample; (10)
      identifying a modulator of (I) comprising contacting (a cell expressing)
      (I) with an agent and determining if the agent has modulated the function
      or activity of (I); (11) identifying an agent that binds to (I)
      comprising contacting (I) with an agent and assaying the mixture to
```

determine whether a complex is formed with the agent bound to (I); (12) a pharmaceutical composition (PC) comprising an agent identified using (I); (13) an isolated human **kinase** peptide (VI) having an amino acid sequence that shares at least 70% **homology** with (S1); and (12) an isolated nucleic acid molecule encoding a human **kinase** peptide, sharing at least 80% **homology** with (S2).

WIDER DISCLOSURE - Also disclosed are: (1) new agents identified by screening assays using (I); (2) kits comprising (III), to detect the presence of a protein in a sample; (3) kits for detecting the presence of a **kinase** nucleic acid in a biological sample; and (4) nucleic acid detection kit, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information of (II).

BIOTECHNOLOGY - Preparation: (I) is prepared by introducing (II) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence (claimed). Preferred Peptide: (VI) shares at lest 90% **homology** with (S1). Preferred Method: In the method for identifying a modulator of (I), the agent is administered to a host cell comprising an expression vector that expresses (I).

ACTIVITY - None given.

MECHANISM OF ACTION - Gene therapy. No supporting data is given.

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a biological condition, to assess normal and aberrant subcellular localization of cells in various tissues in an organism, in pharmacogenomic analysis, for tissue typing and for inhibiting protein function. (V) is useful for producing a **kinase** protein or peptide, conducting cell-based assays involving the **kinase** protein, identifying **kinase** protein mutants and to produce non-human transgenic animals which are useful for studying the function of a **kinase** protein and identifying and evaluating modulators of **kinase** protein activity. (96 pages)

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L18	291	S	E3
L19	1279	S	L15 OR L16 OR L17 OR L18
L20	1	S	L9 AND L19
L21	764	S	L15 AND L19
L22	1	S	L6 AND L19